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स्थापना : ९ जानेवारी १९२७

42. 'देह कुठरिया' चित्रित किन्नरों का संघर्ष
- डॉ. मंजुषा संदिपानराव कोल्हे ---------- 145

43. हिन्दी उपन्यास और किन्नर विमर्श
- प्रा. डॉ. आनंद रणजीत बक्षी ---------- 148

44. हिन्दी उपन्यासों में किन्नर जीवन की त्रासदी (किन्नर केंद्रित उपन्यासों के आलोक में)
- 1) डॉ. शेख़ बेनज़ीर, 2) डॉ. एस. सूर्यावती ---------- 152

45. 'ऐ जिंदगी तुझे सलाम' किन्नर जीवन का यथार्थ चित्रण
- डॉ. नामदेव ज्ञानदेव शितोळे ---------- 155

46. हिंदी उपन्यास और किन्नर विमर्श
- प्रा. डॉ. सतीश दत्तात्रय पाटील ---------- 159

47. हिंदी कथासाहित्य में किन्नर विमर्श
- प्रा.निर्मला लक्ष्मण जाधव ---------- 163

48. समकालीन कथाओं में किन्नर विमर्श
- डॉ. राजू सीताराम पवार ---------- 166

49. हिंदी कहानियों में किन्नर विमर्श
- डॉ. कल्याण शिवाजीराव पाटील ---------- 169

50. गिरिजा भारती कृत अस्तित्व उपन्यास में कृत किन्नर जीवन
- डॉ.दिलीपकुमार रा. गुंजरगे ---------- 173

51. समकालीन हिन्दी उपन्यासों में अभिव्यक्त किन्नर जीवन
- डॉ. सजिना पी. एस. ---------- 176

▲▲▲

हिन्दी उपन्यास और किन्नर विमर्श

प्रा. डॉ. आनंद रणजीत बक्षी
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शोध सार :

समाज की संरचना मानव से होती है । समाज में जो भी प्रत्यक्ष या अप्रत्यक्ष रूप से घटित होता है, वह लिखित दस्तावेज के रूप में साहित्य में समाहित होता आया है । पौराणिक दन्त कथाओं, अतीत से लेकर वर्तमान तक के किस्से कहानियों आदि की उपस्थिति साहित्य में धरोहर के रूप में सुरक्षित रही है । समयानुसार साहित्य ने भी अपने स्वरूप विषय में परिवर्तन किया है । आधुनिक समय विमर्श का अर्थात लिखित चर्चा-परिचर्चा एवं शोध का रहा है । इसमें सामान्य जन से त्यागे गए, प्रताड़ित-शोषित किए गए वर्ग या जाति समूह का गहन एवं विस्तृत अध्ययन है । इनमें स्त्री विमर्श, दलित विमर्श, आदिवासी विमर्श, किन्नर विमर्श प्रमुख रहे हैं। ये सभी विमर्श समाज से परित्यक्त मानवीय अस्मिता के प्रति जन जागृति करने का रहा हैं । किन्नर विमर्श इसी का एक महत्वपूर्ण उदाहरण है । इस आलेख के अंतर्गत हिन्दी उपन्यास और किन्नर विमर्श पर विश्लेषण प्रस्तुत करने का प्रयास किया गया है ।

बीज शब्द : हिन्दी उपन्यास; किन्नर; साहित्य; विमर्श ।

प्रस्तावना :

साहित्य में किन्नर विमर्श से संबंधित अब तक कई लेखन कार्य हुए । कविता, कहानी, उपन्यास, आत्मकथा, संपादित, समीक्षात्मक कार्य आदि लिखे गए सभी उपन्यासों में एक विशेष विषय की भूमिका पर लेखन कार्य हुए हैं । जब विमर्श किसी एक समाज विशेष के उत्थान में कार्य करता है तब उसका समाजिक, धार्मिक, सांस्कृतिक, राजनीतिक अध्ययन के साथ ही साथ शारीरिक, भाषिक, व्यवहारिक, मनोवैज्ञानिक आदि पक्षों का भी अध्ययन करना आवश्यक है । किन्नर जीवन केंद्रित हिंदी उपन्यास के संदर्भ में 2002 में मयमदीपफ उपन्यास के प्रकाशन के लगभग 10-12 वर्षों के पश्चात् इस विषय पर उत्तरोतर लेखकों का ध्यान आकृष्ट हुआ जो अब समकालीन परिप्रेक्ष्य में चतुर्दिश बहस का विषय बना हुआ है, जबकि मयमदीपफ उपन्यास के 6 वर्ष बाद ही वर्ष 2008 में मर्मै भी औरत हूँफ उपन्यास प्रकाशित हो चुका था । इसका सीधा अर्थ यह है कि इस विषय पर 5-6 उपन्यास प्रकाशित हो गए थे उसके बाद भी 'किन्नर विमर्श' के रूप में लंबा समय लगा ।

मूल शोध आलेख :

भारतीय समाज में शारीरिक या मानसिक विकृति के साथ जन्मे अधिकतर इंसान सदियों से उपेक्षित रहे हैं। इसी समाज में किसी विकृत या अक्षम अवस्था में भी पूर्णतया उसका भोग कर लेने की प्रवृत्ति मानसिक कुंठा की शिकार से पीड़ित होती है जो लाईलाज है । इसके विपरीत विषम परिस्थितियों में भी किसी को अपनाकर उस पर सर्वस्व न्योछावर कर देने की संस्कृति भी निहित है । यमदीप उपन्यास के कथानक की शुरुआत भी कुछ इसी आधार पर होती है । यमदीप उपन्यास के कथानक के बीजपन की शुरुआत सन् 1991 में नीरजा जी की बेटी कुहू के जन्म के कुछ महीने पहले, उनके कालोनी में आए हिजड़ा समुदाय द्वारा उन्हें आशीर्वाद देते हुए नेग के संबंध में औपचारिक बातों से हुई। इस संकल्प के पश्चात् सन् 1991 से शुरू हुआ लेखन कार्य सन् 2002 में पुस्तक के रूप में प्रस्तुत हुआ । यमदीप उपन्यास का सबसे महत्वपूर्ण तथ्य यह है कि इस उपन्यास में 'हिजड़ा' शब्द का ही प्रयोग किया गया है जबकि अन्य उपन्यासों में 'किन्नर' शब्द का भी प्रयोग किया गया है । वस्तुतः यह उपन्यास किन्नर विमर्श के तौर पर ही लिखा गया और किन्नर विमर्श के रूप में ही लोकप्रिय भी हुआ परंतु इसके कथानक में हिजड़ा वर्ग के साथ ही स्त्री विमर्श भी समान रूप से निहित है। उपन्यास की मुख्य नायिकाएँ, नाज़बीबी हिजड़ा समुदाय और मानवी स्त्री के अस्तित्व का प्रतिनिधित्व करते हुए सामाजिक स्वीकार्यता के लिए प्रयासरत हैं । हिजड़ा और स्त्री जीव के दैहिक तथा मानसिक उत्पीड़न की समस्याएँ इस उपन्यास के केंद्र बिंदु हैं । यमदीप उपन्यास की विशेषता यह भी है कि इस उपन्यास में किन्नर की बजाय महिजड़ाफ नाम का संबोधन किया गया है ।

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''शारीरिक जननांग विकलांगता के कारण अपने परिवारजनों से दूर किन्नर व्यक्ति के विस्थापित जीवन और उनके मानवीय गुणों को सामाजिक और लोकतंत्रीकरण से जोड़ते हुए लिखा गया किन्नर विमर्श पर केंद्रित प्रथम उपन्यास यमदीप ही है । इस उपन्यास की चर्चा व्यापक तौर पर लंबे अंतराल के बाद ही हुई ।''[1]

अनुसूया त्यागी द्वारा लिखित चिकित्सकीय अनुभवों पर आधारित तथा वास्तविक घटना पर लिखा गया उपन्यास मर्मै भी औरत हूँफ किन्नर विमर्श अध्ययन के लिये प्रमाणिक तौर पर महत्वपूर्ण है । जननांग विकृति के साथ जन्मी दो बहनें जिनका शल्यक्रिया द्वारा ईलाज डॉक्टर और लेखिका अनुसूया त्यागी जी द्वारा किया गया था । विश्वसनीयता के आधार पर पात्रों के नाम बदल दिये गए हैं । लेखिका द्वारा किए गए उपचार के उपरांत पात्रों के जीवन में घटित सुनहरे भविष्य की आशावादी कल्पना के साथ कथानक का समापन किया गया है ।[2]

लेखिका और स्त्री रोग विशेषज्ञ डॉक्टर अनुसूया त्यागी द्वारा लिखित 'मैं भी औरत हूँ' यह उपन्यास उनके नर्सिंग होम में उपचार कराने आयी दो बहनों की वास्तविक कहानी है । दोनों ही बहनों की शारीरिक विकृति को चिकित्सा विज्ञान की सहायता पूरी करने की कहानी है । उपन्यास के प्राक्कथन में लेखिका स्पष्ट कहती हैं कि ''इस उपन्यास की दोनों नायिकाओं- रोशनी और मंजुला (नाम वास्तविक नहीं है) को लेकर उनके माता-पिता एक वर्ष पहले मेरे पास आए थे। फिर मैंने दोनों का ऑपरेशन किया । यह वास्तविक, सत्य घटना है... उपन्यास में उनका भविष्य मेरी कल्पना है ।'' लेखिका ने इन दोनों ही बहनों के जो भविष्य की कल्पना की है वह समाज में इनके प्रति सकारात्मक दृष्टिकोण अपनाने का ही एक मार्ग प्रशस्त करने का प्रयास किया है ।

समाजोन्मुखी कथाकार महेंद्र भीष्म जी द्वारा लिखित मर्मै पायल... (किन्नर गुरु पायल सिंह के जीवन-संघर्ष पर आधारित) उपन्यास लखनऊ की प्रतिष्ठित किन्नर गुरु पायल सिंह की जीवनी है । इस उपन्यास की जीवंत पात्र पायल सिंह वर्ष 2001 में लखनऊ पश्चिम क्षेत्र से राष्ट्रवादी कम्युनिस्ट पार्टी की प्रत्याशी के तौर पर विधानसभा चुनाव में शामिल हुई थी । वर्ष 2010 लखनऊ में ही पायल सिंह ने 'पायल फाउंडेशन' की स्थापना कर समाजहित में अपना योगदान दे रहीं है । फिल्म क्षेत्र में रुचि रखनेवाली और अभिनय कला में पारंगत पायल ने उत्तरोत्तर प्रगति करते हुए कई फीचर फिल्म के निर्देशन के साथ ही मुख्य भूमिका भी अदा की है । किन्नर पायल सिंह के इन प्रगतिशील कार्यों से प्रभावित हुए रचनाकार महेंद्र भीष्म जी ने पायल सिंह के जीवन को पन्नों पर उकेरा । हिंदी साहित्य में किन्नर विमर्श पर केंद्रित 'मैं पायल... किन्नर गुरु पायल सिंह के जीवन- संघर्ष पर आधारित)' प्रथम जीवनीपरक उपन्यास है जिसमें काल्पनिकता को नहीं वरन् यथार्थ को लिपिबद्ध किया गया है ।[3]

साहित्य को अभिव्यक्ति का माध्यम मानने वाले लेखक प्रदीप सौरभ ने तीसरी ताली उपन्यास के पात्रों के वास्तविक नाम के साथ लिखकर उपन्यास की प्रमाणिकता की पुष्टि ही की है। वास्तविकता का बोध कराने वाली कहानी लिखना एवं वास्तविकता को कहानी के साँचे में ढालकर लिखना दोनों में अंतर है और किसी विषय पर गहन अध्ययन और अन्वेषण कर उपन्यास लिखना प्रदीप सौरभ की कृतियों की विशेषता है ।

प्रदीप सौरभ ने 'तीसरी ताली' उपन्यास की पारदर्शिता के लिए पहले पन्ने पर ही लिखा है कि मुन्नी मोबाइलफ की तरह ही इस उपन्यास के नायक और खलनायक भी काल्पनिक नहीं हैं । 'तीसरी ताली' कृति के लिए ब्रिटिश संसद में प्रदीप सौरभ जी 'अठारहवाँ इंदु अंतर्राष्ट्रीय इंदु कथा सम्मान' से सम्मानित है । एक लेखक की कलम और पत्रकार की स्याही से लिखा गया मतीसरी तालीफ उपन्यास किन्नर समाज की अन्तः पीड़ा का गहराई से अंकन करता है ।[4]

बीसवीं सदी के बाद मुख्य रूप से नए उभरते लेखकों, पत्रकारिता और अध्यापन क्षेत्र से संबंधित शिक्षाविद जैसे कृतिकारों ने उपन्यास के आवरण से किन्नर समाज को लिखित रुप में चित्रित करने का कार्य किया। 'नई दुनिया' समाचार पत्र की फीचर संपादक तथा वरिष्ठ पत्रकार एवं लेखिका निर्मला भुराड़िया 'रक्तसूर्य सम्मान' से भी सम्मानित हो चुकी हैं । विविध विधाओं पर यथार्थ एव अन्वेषणपरक लेखन कार्य करने वाली निर्मला भुराडिया 'लाईफ साइंस' से पदवी प्राप्त हैं ।[5]

लेखिका गिरिजा भारती के कृतित्व का पहला उपन्यास 'अस्तित्व' लेखिका को हुए समाजिक अनुभवों का प्रतिफल है जो यथार्थपरक घटना पर आधारित है । किन्नर विमर्श पर हुई एक वेबगोष्ठी में इसे स्पष्ट करती हैं कि मैंने ये कहानी कोई बनावटी नहीं बनाई है... ये मेरी काल्पनिक कहानी नहीं है... हम समाज में कुछ देखते हैं तभी हमें कुछ करने की प्रेरणा मिलती है और मैंने समाज में कुछ चीजें देखीं जो नहीं होनी चाहिए तभी मुझे इसे लिखने की मन में प्रेरणा जागी और मैंने इसे लिखा ।'' लेखिका द्वारा 128 पृष्ठों का यह उपन्यास सारगर्भित एवं त्वरित समाप्ति तरीके से लिखा गया प्रतीत होता है ।

किन्नर व्यक्ति जीवन को कहानी के प्रारूप में 'दरमियाना' लिखनेवाले सुभाष जी उपन्यास की भूमिका में लिखते हैं कि

इस कहानी की विषयवस्तु ने न जाने कितने वर्ष लगाये होंगे रचना बनने के लिए । दरअसल, बचपन की वही जिज्ञासाएँ मुझे बार-बार इनके करीब ले गई। आज भी ले जाती हैं । यूँ अन्य रचनाएँ तो इधर-उधर छपने लगी थीं, मगर तत्कालीन प्रतिष्ठित साहित्यिक पत्रिका मसारिकाफ के एक अक्टूबर 1980 के अंक में, 'दरमियाना' को ससम्मान प्रकाशित किया गया। मसारिकाफके तत्कालीन संपादक कन्हैया लाला नंदन सहित सभी संपादकीय सहयोगियों ने एवं जैनेन्द्र कुमार, विष्णु प्रभाकर, अजित कुमार, डॉ. नरेंद्र कोहली तथा अन्य सभी साहित्यकारों ने- 'दरमियाना' को. इस विषय पर लिखी गई हिदी की पहली कहानी माना था । सभी को यह आश्चर्य था कि जो 'विषय अभी तक साहित्य के योग्य ही नहीं समझा गया', उस विषय पर 'इस लड़के' ने लिखने का साहस किया। लेखक ने किन्नर शब्द का प्रयोग ना कर 'दरमियाना' संबोधित किया है । वर्ष 2018 में प्रकाशित यह 'दरमियाना' उपन्यास वर्ष 1980 के मदरमियानाफकहानी का विकसित रूप है ।

वर्ष 2018 में प्रकाशित 'आधा आदमी' उपन्यास लेखक राजेश मलिक के 17 वर्षों के शोध का प्रतिफल है । किन्नर समाज की आंतरिक और रहस्यमय जीवन की पड़ताल करना बेहद जटिल कार्य रहा है । उपन्यास लेखन हेतु आवश्यक शोध प्रक्रिया के आरंभ में लेखक का मन लेखक को आगाह करता है-कहीं तुम्हारा दिमाग तो नहीं फिर गया। क्या तुम भूल गए, दिपिकामाई ने क्या कहा था कि हम अपने समाज की बातें किसी को नहीं बताते । भूल के भी इनके पास मत जाना वरना पछताने का भी मौका नहीं मिलेगा । तुमने कभी सोचा? इस सब्जेक्ट पर और राइटरों ने कलम क्यों नहीं उठाई? क्योंकि वे जानते थे कि इनके बीच जाना और शोध करना खतरे से खाली नहीं हैं । अपनी भलाई चाहते हो तो इनसे दूर रहो। यह केवल लेखक का मन नहीं बल्कि समाज का मन है जिसे लेखक समाज के ही समक्ष प्रस्तुत करता है।

किन्नर व्यक्ति का समाज में स्वयं को स्वतंत्र रूप से अभिव्यक्त ना कर पाना यह प्रमुख समस्या रही है जिसके कारण लोगों में इनके प्रति डर, अचंभा, उपहास, उपेक्षा, यौन कुंठा आदि भावनाओं की जिज्ञासा प्रबल होती दिखाई देती है। सब कुछ जान लेने का भाव एक मानसिक प्रवृत्ति है इसके आधार पर ही कई समाज की कई बंद कड़ियाँ खुलती रही हैं। ज्ञानदीप की यही जिज्ञासा दीपिकामाई के जीवन के अनछुए पहलुओं को प्रकट करती हैं । किन्नर विमर्श के अंतर्गत लगभग जितने भी लेखन कार्य हुए उनमें से यह मआधा आदमीफ उपन्यास इसलिए भी विशेष है क्योंकि इसका नायक पात्र दीपक पुरुष होने के बावजूद भी संघर्षमय जीवन जीने की जद्दोजहद में किन्नर बनने का रास्ता अपनाता है ।

साहित्य के माध्यम से किन्नर समुदाय की समाज में स्वीकार्यता दर्ज कराने का कार्य लेखकों ने किया है । उपरोक्त सभी उपन्यासों में से जिनके लेखक स्वयं पत्रकारिता अथवा शोध लेखन जैसे क्षेत्र से संबंधित हैं वे उपन्यास किन्नरों को भी विमर्श से जुड़ने तथा साहित्यिक मंच पर चर्चाओं का भागीदार बनाते हैं । उनके पात्र काल्पनिक नहीं बल्कि वास्तविक हैं जिनसे मिलकर पात्रों के जीवन को करीब से समझा जा सकता है, अनुभव लिया जा सकता है । इसका एक कारण उन लेखकों का केवल लेखन तक सीमित ना होकर प्रत्यक्ष एवं तटस्थ विचार-विमर्श करना रहा है । इनमें कुछ उपन्यास ऐसे भी हैं जो केवल प्राप्त जानकारियों अथवा सुनी-सुनाई कहानियों का काल्पनिक घटनाओं का हिस्सा भर है । इन उपन्यासों में किन्नर समाज से जुड़ी रस्मों, जीवन कलाओं, नियमों, रीति-रिवाजों का मिला-जुला स्वरूप दिखाई देता है । एक किन्नर व्यक्ति के व्यक्तिगत एवं सामूहिक विषमताओं, पीड़ाओं इत्यादि को वर्णित किया गया है ।

निष्कर्ष :

कथा साहित्य में पितृसत्तात्मक सोच के कारण पिता के उग्र और अमानुषिक व्यवहार पर सशक्त कानूनी कारवाई होनी चाहिए । ताकि घर से अलिंगीय बच्चों का निष्कासन करने में रोकथाम लगें । किन्नरों को संवैधानिक कानूनी व्यवस्था के प्रति जागरूक होने की अति आवश्यकता है । उन्हें मानवीय अधिकारों के तहत् समाज का प्रतिरोध करना होगा । सरकार से शिक्षा, संपत्ति, सुरक्षा अधिकारिक रूप से माँग करने की आवश्यकता है । किन्नर समुदाय को स्वावलंबी होकर पारम्परिक धंधे के साथ रोजगार के क्षेत्र में आगे बढ़ने और मेहनत करनी होगी । अपनी मौलिक कला और कौशल को जीविकोपार्जन का माध्यम बनाने के साथ लघु और कुटीर उद्योग में आगे बढ़ने का प्रयास करना चाहिए । शिक्षित किन्नरों को साहित्य और सिनेमा के क्षेत्र से जुड़कर अपने समुदाय की दशा और दिशा के बारे में काम करने की आवश्यकता है । किन्नर समुदाय के शिक्षित और प्रतिष्ठित सदस्यों को अपने समुदाय के रीति-रिवाज, संस्कार, भाषा को प्रचलित करने की पहल विभिन्न मंच और माध्यमों से करनी चाहिए । समुदाय में व्याप्त रूढ़ग्रस्त धारणाओं को तोड़कर समाज को राष्ट्रीय उत्थान में सफलतापूर्वक सहयोग करना चाहिए ।

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-88 36. **Employability of Business Education in India** 175-179
Dr. Vivek M. Morey

-92 37. **What is National Education Policy 2020: What's the benefit of NEP to stake holders (Parent, Student, Teacher) as a Higher Education Institute?** 180-185
-97 Prof. Ashish Rameshlal Kanhu

38. **Job Satisfaction and Impact of NEP on The Creation of New Job** 186-189
102 Shri. Bharat S. Deshmukh

39. **NEP 2020 and Online Education - Benefits and Challenges** 190-195
-107 Dr. Ashish P. Mohata

40. **An Efficient Architecture For Mobile Web Services in Cloud Environment** 196-201
-112 Dr. Dudhe Anil A., Dr. Sherekar S.S.

41. **Impact of New Education Policy 2020 on Higher Education** 202-207
Dr. Rupesh S. Mankar

-117 42. **Comparison of National Education Policy 1986 And New Education Policy** 208-211
Dr. Sanjivani K. Parate

43. **NEP 2020: Features of NEP 2020 and Role of Teacher in NEP 2020** 212-216
-122 Dr. Santosh P. Rathod

44. **भारतातील आरक्षण आणि राजकारण** 217-219
-128 प्रा. डॉ. अरुण मुकुंदराव शेळके

45. **भारत की नई शिक्षा नीति – विशेषताएँ, गुण एवं दोष** 220-224
डॉ. जे. एस. सवाईथूल

-132 46. **राष्ट्रीय शिक्षा नीति के माध्यम से भारतीय भाषाओं कला और संस्कृति का संवर्धन** 225-227
-137 डॉ. आनंद आर. बक्षी

■ ■ ■

-142

-147

-151

-161

-165

-170

-174

राष्ट्रीय शिक्षा नीति के माध्यम से भारतीय भाषाओं कला और संस्कृति का संवर्धन

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सारांश :

भारतीय कला एवं संस्कृति का संवर्धन न सिर्फ राष्ट्र बल्कि व्यक्तियों के लिए भी महत्वपूर्ण है। बच्चों में अपनी पहचान और अपनेपन के भाव तथा अन्य संस्कृतियों और पहचानो की सराहना का भाव पैदा करने के लिए सांस्कृतिक जागरूकता और अभिव्यक्ति जैसी प्रमुख क्षमताओं को बच्चों में विकसित करना जरूरी है। बच्चों में अपने सांस्कृतिक इतिहास, कला, भाषा एवं परंपरा की भावना और ज्ञान के विकास द्वारा ही एक सकारात्मक सांस्कृतिक पहचान और आत्म सम्मान बच्चों में निर्मित किया जा सकता है। अतः व्यक्तिगत एवं सामाजिक कल्याण के लिए सांस्कृतिक जागरूकता और अभिव्यक्ति का योगदान महत्वपूर्ण है। संस्कृति का प्रसार करने का सबसे प्रमुख माध्यम कला है। कला सांस्कृतिक पहचान, जागरूकता को समृद्ध करने और समुदायों को उन्नत करने के अलावा व्यक्तियों में सृजनात्मक क्षमताओं को बढ़ाने तथा व्यक्तिगत प्रसन्नता को बढ़ाने के लिए जानी जाती है। व्यक्तियों का सृजनात्मक विकास के साथ सांस्कृतिक विकास होना भी जरूरी है जिसके लिए सभी प्रकार के भारतीय कलाएं प्रारंभिक बाल्यावस्था, देखभाल व शिक्षा से आरंभ करते हुए शिक्षा के सभी स्तरों पर छात्रों को प्रदान की जानी चाहिए।

शोध संज्ञा– राष्ट्रीय शिक्षा नीति, भारतीय भाषा और कला एवं संस्कृति का संवर्धन

प्रस्तावना –

पंडित मदन मोहन मालवीय ने कहा है-'' भारतीय सभ्यता और संस्कृति की विशालता और उसकी महना तो संपूर्ण मानव के तादात्म्य संबंध स्थापित करने अर्थात वसुधैव कुटुंबकम की पवित्र भावना में निहित है'' भारतीय सभ्यता और संस्कृति को समझने के लिए हमें भारत की भाषा ,धर्म ,संप्रदाय भारतीय समाज ,भारतीय पहनावा, भारतीय साहित्य, भारतीय दृश्यकला, भारतीय मनोरंजन और खेल, लोकप्रिय मीडिया, भारतीय दर्शनशास्त्र आदि से भली-भांति परिचित होना होगा भारतीय संस्कृति में निम्नलिखित विशेषताएं परिलक्षित होती है-

१. भारतीय संस्कृति में सहनशीलता और ग्रहणशीलता पाई जाती है।

२. भारतीय संस्कृति ''वसुदैव कुटुम्बकम'' की भावना पर आधारित है।

भारतीय संस्कृति की सुरक्षा एवं संरक्षा के लिए निम्न बातों पर ध्यान देना होगा-

१. अपनी प्राचीन भाषाओं को बचाने का प्रयास करना।

२. अपनी कला और तकनीक को दूसरों को शेयर करना।

३. सामाजिक और राष्ट्रीय महत्व के उत्सव का आयोजन करना।

४. समुदाय और समाज के अन्य सदस्यों के साथ मिलजुल कर रहना

कोठारी आयोग शिक्षा नीति की प्रमुख सिफारिशें निम्नलिखित हैं -

१. शिक्षा राष्ट्रीय महत्व का विषय है.

२. १४ वर्ष तक के बच्चों को निशुल्क एवं अनिवार्य शिक्षा ,शिक्षकों की योग्यता एवं बेहतर प्रशिक्षण

३. प्राचीन संस्कृत भाषा भारतीय संस्कृति और विरासत का अनिवार्य हिस्सा है

४. शिक्षा पर केंद्रीय बजट का ६% व्यय हो.

५. माध्यमिक स्तर पर त्रिभाषा सूत्र का प्रावधान हो

इसके बाद सन् १९८६ में नई शिक्षा नीति को अपनाया गया जिसकी प्रमुख विशेषताएं निम्नलिखित है -

१. असमानताओं को दूर करना -भारतीय महिलाओं, अनुसूचित जाति, अनुसूचित जनजाति समुदाय के लिए शैक्षिक स्तर की बराबरी पर विशेष जोर देना

२. प्राथमिक स्कूलों को बेहतर बनाने के लिए ऑपरेशन ब्लैक बोर्ड लांच किया गया ३) इंदिरा गांधी राष्ट्रीय मुक्त विश्वविद्यालय के साथ ओपन यूनिवर्सिटी प्रणाली का विस्तार किया गया

सन १९९२ में राष्ट्रीय शिक्षा नीति में फिर से संशोधन किया गया तकनीकी प्रवेश के लिए राष्ट्रीय स्तर पर प्रवेश परीक्षा का आयोजन जैसे अनेक महत्वपूर्ण सुधार किए गए इसके बाद नई शिक्षा नीति २०२० बनाई गई जिस की कुछ विशेषताओं पर प्रकाश डालते हैं-

१. पूर्व प्राथमिक स्तर पर संज्ञानात्मक विकास

२. प्राथमिक स्तर पर समावेशी शिक्षा

३. माध्यमिक में नवाचारी शिक्षा

४. उच्च स्तर पर नवीन प्रणाली की स्थापना

नई शिक्षा नीति की सबसे बड़ी विशेषता यह है कि इसमें कला, संस्कृति और भाषा के माध्यम से मनुष्य की सृजनात्मक क्षमता की जागृति पर बल दिया गया है । भाषा अभिव्यक्ति का माध्यम ही नहीं बल्कि किसी राष्ट्र के स्वाभिमान तथा प्राचीन संस्कृति की संवाहक भी होती है । नई शिक्षा नीति में इस बात का जोर दिया गया है कि मौलिक विचार अपनी मातृभाषा में ही आते हैं। भाषाओं में सतत प्रवाह बनाए रखने के लिए गुणवत्तापूर्ण अधिगम एवं प्रिंट सामग्री की जरूरत होती है। भाषाओं के शब्द भंडार लगातार अपडेट होने चाहिए इस हेतु दिए गए मुख्य सुझाव निम्नलिखित है-

१) मूल्यपरक शिक्षा के लिए इंफ्रास्ट्रक्चर को बढ़ाना होगा

भारत संस्कृति का समृद्ध भंडार है- यहां की कला, साहित्य, कृतियों ,प्रथाओं ,भाषा अभिव्यक्तियों, ऐतिहासिक एवं सांस्कृतिक धरोहर के स्थलो इत्यादि में परिलक्षित होता हुआ दिखता है। भारत की सांस्कृतिक संपदा का संरक्षण, संवर्धन एवं प्रसार देश की उच्चतर प्राथमिकता होनी चाहिए क्योंकि यह देश की पहचान के साथ-साथ इसकी अर्थव्यवस्था के लिए भी बहुत महत्वपूर्ण है।

२) सुयोग्य अध्यापकों की नियुक्ति हो

भारतीय कला एवं संस्कृति का संवर्धन न सिर्फ राष्ट्र बल्कि व्यक्तियों के लिए भी महत्वपूर्ण है बच्चों में अपने सांस्कृतिक इतिहास, कला, भाषा एवं परंपरा की भावना और उनके विकास द्वारा ही एक सकारात्मक संस्कृति पहुंचा और आत्मसम्मान निर्मित किया जा सकता है। इसके लिए सुयोग्य अध्यापकों की नियुक्ति होना जरूरी है।

३) कृषि एवं रोजगारपरक शिक्षा हो

उच्चतर शिक्षा में कला संस्कृति और भाषा के क्षेत्रों में ऐसे कार्यक्रम बनाने से रोजगार और गुणवत्तापूर्ण अवसर भी पैदा होंगे। जो इन योग्यताओं का प्रभाव कारी उपयोग कर पाएंगे।

४) भारतीय भाषा कला व संस्कृति का प्रचार हो

संस्कृति का प्रचार करने का सबसे प्रमुख माध्यम कला है व्यक्तियों की प्रसन्नता और सांस्कृतिक पहचान वह महत्वपूर्ण कारण है। जिसके लिए सभी प्रकार की भारतीय कलाएं, बाल्यावस्था देखभाल व शिक्षा के सभी स्तरों पर छात्रों को प्रदान की जानी चाहिए।

५) बच्चों में सांस्कृतिक जागरूकता और अभिव्यक्ति क्षमता विकसित करना

भाषा निसंदेह कला एवं संस्कृति से अटूट रूप से जुड़ी हुई हैं। संस्कृति हमारी भाषाओं में समाहित है। साहित्य, नाटक, संगीत, फिल्म ,आदि के रूप में कला की पूरी तरह सराहना बिना भाषा के संभव नहीं है। संस्कृति के संरक्षण, संवर्धन और प्रसार के लिए हमें संस्कृति की भाषाओं का संरक्षण और संवर्धन करना होगा।

६) पारंपरिक ज्ञान को पाठ्यपुस्तक में शामिल किया जाए

शास्त्रीय, आदिवासी और लुप्तप्राय भाषाओं सहित सभी भारतीय भाषाओं को सुरक्षित और बढ़ावा देने के प्रयास नए जोश के साथ किए जाएंगे।

७) कलात्मक संगीत दर्शन आदि को बढ़ावा दिया जाए

स्थानीय संगीत, कला ,भाषाओं एवं हस्तशिल्प को प्रोत्साहित करने के लिए तथा यह सुनिश्चित करने के लिए कि छात्र जहां अध्ययन कर रहे हो वहां की संस्कृति एवं स्थानीय ध्यान को जान सके, उत्कृष्ट स्थानीय कलाकारों एवं हस्तशिल्प व्यक्तियों को अतिथि शिक्षक के रूप में नियुक्त किया जाएगा।

८) रचनात्मक लेखन की कला विकसित हो

उच्चतर शिक्षा व्यवस्था के अंतर्गत अनुवाद और विवेचना, कला और संग्रहालय प्रशासन, पुरातत्व, कलाकृति संरक्षण, ग्राफिक डिजाइन एवं

वेब डिजाइन के उच्चतर गुणवत्तापूर्ण कार्यक्रम एवं डिग्रियों का सृजन भी किया जाएगा।

९) संग्रहालय, पुरातत्व का संरक्षण हो

भारत की सांस्कृतिक संपदा का संरक्षण, संवर्धन एवं प्रसार देश की उच्च प्राथमिकता होना चाहिए, क्योंकि यह देश की पहचान के साथ-साथ इसकी अर्थव्यवस्था के लिए भी महत्वपूर्ण है।

१०) शैक्षिक संस्थान के छात्रों को पर्यटन कराया जाए

अपनी कला एवं संस्कृति को संरक्षित करने और बढ़ावा देने के लिए विभिन्न भारतीय भाषाओं में उच्चतर गुणवत्ता वाली सामग्री विकसित करना, कलाकृतियों का संरक्षण करना, संग्रहालय और विरासत या पर्यटन स्थलों को चलाने के लिए उच्चतर योग्यता प्राप्त व्यक्तियों का विकास करना जिससे पर्यटन उद्योग को भी काफी मजबूती मिल सके।

११) आठवीं अनुसूची में उल्लिखित भाषाओं के लिए अकादमी स्थापित की जाए

भारतीय भाषाओं के शिक्षण और अधिगम को स्कूल और उच्चतर शिक्षा के प्रत्येक स्तर के साथ एकीकृत करने की आवश्यकता है। भाषाएं प्रासंगिक और जीवंत बनी रहे इसके लिए इन भाषाओं में उच्चतर गुणवत्तापूर्ण अधिगम एवं प्रिंट सामग्री का सतत प्रवाह बने रहना चाहिए।

१२) लुप्तप्राय भाषा, कला, संस्कृति को सुरक्षित किया जाए

मुदलियार आयोग, कोठारी आयोग, नई राष्ट्रीय शिक्षा नीति-१९८६ में भारतीय भाषाओं को समुचित ध्यान और देखभाल नहीं मिल पाई। जिसके तहत देश ने विगत ५० वर्षों में ही २२० भाषाओं को खो दिया है यूनेस्को ने १९७ भारतीय भाषाओं को लुप्त घोषित किया है। विभिन्न भाषाएँ लुप्त होने की कगार मै हैं इसीलिए यहां भाषाएं को पाठ्यपुस्तक में शामिल किया जाए।

१३) संस्कृत भाषा को मुख्यधारा में लाने का प्रयास

संस्कृत भाषा के महत्वपूर्ण योगदान तथा विभिन्न विधाओं एवं विषयों के साहित्य, सांस्कृतिक महत्व, वैज्ञानिक प्रकृति के चलते संस्कृत को केवल संस्कृत पाठशाला एवं विश्वविद्यालयों तक सीमित ना रखते हुए इसे मुख्यधारा में लाया जाएगा। स्कूलों में त्रिभाषा फार्मूला के तहत एक विकल्प के रूप में साथ ही साथ उच्चतर शिक्षा में भी इसे पृथक रूप से नहीं पढ़ाया जाएगा बल्कि रुचि पूर्ण तरीके से पढ़ाया जाएगा।

समारोप

इस प्रकार नई शिक्षा नीति २०२० में लुप्त हो रही बोली जाने वाली भाषाओं सहित सभी भारतीय भाषाओं और उनसे जुड़ी समृद्ध स्थानीय कला और संस्कृति को संरक्षित करने के लिए सभी भारतीय भाषाओं और उनसे जुड़ी स्थानीय कला और संस्कृति को विभिन्न रूपों में लिखा जाएगा। २०२० में माध्यम। भाषा, कला और संस्कृति के विकास के लिए विभिन्न मंच उपलब्ध होंगे। ऐसे प्लेटफॉर्म को समृद्ध बनाने के लिए विश्वविद्यालय और उनके शोध समूह एक दूसरे के साथ और देश भर के समुदायों के साथ काम करेंगे। उच्च शिक्षा प्रणाली के तहत भारतीय भाषा, कला और संस्कृति का अध्ययन करने के लिए सभी उम्र के लोगों के लिए छात्रवृत्ति की स्थापना की जाएगी।

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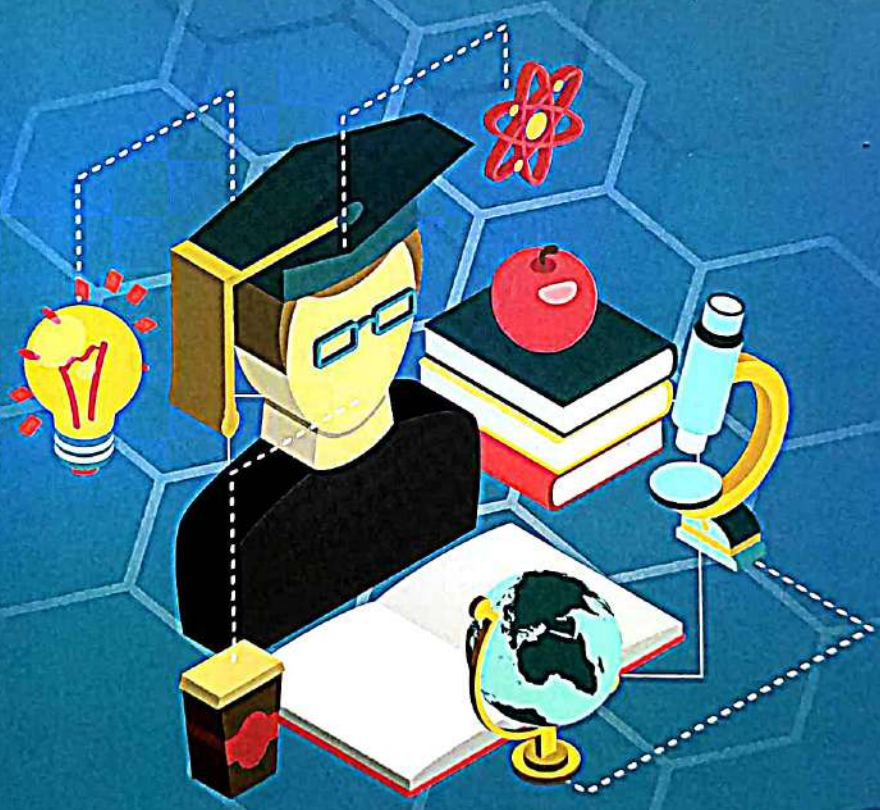
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Index

Sr. No.	Research Paper & Author	Page No.
01.	**Skill Based Education in NEP 2020: An Overview** Dr Bandu Jamnik	01-03
02.	**Challenges of NEP 2020 : Reference to the Academic & Non-academic Integration in Diverse Socio-Economic Background** Dr Rekha Kalbande	04-07
03.	**New Education Policy2020: Challenges before Studentsand Teachers** Dr Indal G. Jadhav	08-12
04.	**Electronic Commerce and Management: A Study on Challeneges in An Emerging Economy** Dr. Piyush U. Nalhe	13-19
05.	**Bridging the Linguistic Gulf: Enhancing English Language Proficiency and Engagement in Undergraduate Students from Rural and Backward Areas** Dr. Raheel K. Quraishi	20-24
06.	**Advancements in Molecular Simulation Techniquesfor Understanding Complex Systems : A Comprehensive eview** Surya Pratap Singh	25-31
07.	**National Education Policy 2020 and Online and Digital Education in the subject of Law** Prof. Hemesh Nandkishor Joshi	32-36
08.	**Human Resource Management (HRM) and Role of Teachers with respect to NEP 2020** Dr. Vasudev N. Joshi	37-41
09.	**NEP 2020 and Commerce Education** Dr.Pradip.S.Anantwar	42-45
10.	**Challenges Of National Education Policy: 2020** Dr. Suresh Namdeo Gawai	46-53
11.	**Challenges of NEP 2020-A Study** Dr. Vivek V. Patil	54-58
12.	**The Challenges and Ways of Vocationalisation of Commerce Education** Dr. Deepak Dattatray Nilawar	59-62
13.	**Skill based Education in NEP- 2020: a review** Dr.Sachin Kadu	63-68
14.	**The Evolving Role of Teachers in India's New Education Policy 2020** Dr. Vyankatesh Digambarrao More	69-71
15.	**A New Path Way in NEP 2020 : Stem Education** Dr.Rachna A.Rathi	72-76
16.	**NEP 2020 : Skill Based Education** Ku.Priti Madhukar Naphade	77-81
17.	**Impact Of Nep On The Creation of New Jobs** Miss. Priyanka Mahendrasing Pardeshi, Dr. Avinash S. Nile	82-85

18. **A Study of New Education Policy-2020 Challenges of Teachers and Students** 86-88
Dr. Saddam R. Sayyad

19. **Impact Of National Education Policy 2020** 89-92
Dr.P.N.Ladhe

20. **NEP 2020: A Tool To Make India Superpower** 93-97
Dr.Gayatri Sanjay Tiwari

21. **A Review of Principles and Issues of NEP 2020** 98-102
Dr. Anand P. Wadwale

22. **Value Education and Teacher** 103-107
Dr. Bapurao Dinaji Watode

23. **National Education Policy 2020: A Concern for Higher Education and Management Education** 108-112
Dr. Gayatri S. Chawale

24. **NEP 2020 and Higher Learning Institutions: A Comprehensive Analysis of College Involvement** 113-117
Dr. Lalchand Damodar Bodile

25. **Skill Enhancement and Teachers in Education** 118-122
Dr. Pravin P. Kulkarni

26. **A Critical Study Of NEP 2020: Issues, Approaches, Challenges, Oppertunities And Criticism** 123-128
Dr. Subhash P. Jadhao

27. **New Educaton Policy 2020 and Its Challenges** 129-132
Ms. Komal Ashok Gupta

28. **A Comparative Study of Old Education Policy and New Education Policy 2020** 133-137
Mr. Bhushan Shrirampant Mangate

29. **National Education Policy 2020: A Concern for Management Education** 138-142
Prof. Dr. Rupesh M. Kurhekar

30. **Indian Higher Education and its Challenges** 143-147
Prof. Rahul Gayakwad

31. **Environmental Attunement In Yoga, Physical Education And Sport** 148-151
Dr. Sandeep Gadadane

32. **Exploring All the Features And User Concerns Of Home Away Your Ultimate Housing Solution** 152-161
Anupam Pandey, Yash Bambal, Sakshi Bhor, Karn Datta Godse

33. **New Education Policy 2020, A Journey Toward A More Holistic and Multidisciplinary Education** 162-165
Dr. B. N. Mahajan

34. **National Education Policy 2020: A Catalyst for Skill Based Education** 166-170
Dr. Shivcharan. L. Kottewar

35. **Upcoming Challenges of New Education Policy 2020** 171-174
Dr. Vivek H. Meshram

New Education Policy 2020, A Journey Toward A More Holistic and Multidisciplinary Education

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Abstract:

To mark the completion of two years of transformational reforms in the education sector under the National Education Policy, 2020 (NEP), theme-based webinars on various aspects of the National Education Policy, 2020 are being organized at various places in India. One of the most important areas of the NEP is to include multidisciplinary and holistic education. Today the University Grants Commission is emphasizing multidisciplinary and holistic education. India has had a long tradition of holistic and multidisciplinary education since the time of Taxila and Nalanda. In ancient India, attention was paid to the development of the overall personality. Today, the government is stressing on the need to recreate that model of education, where every aspect of life is empowered. Now the student will not be confined within the boundaries of science, commerce, and humanities. In the 21st century, qualities such as the ability to think outside of the box, critical thinking, effective communication, collaboration, technical skills, and life skills should be developed in students. The role of NEP, 2020 will be important in realizing a self-reliant India and the role of institutions, grants, and cooperation between each other is essential in realizing multidisciplinary education. In this research paper, the new National Education Policy 2020, a journey towards more holistic and multidisciplinary education, this topic has been selected for research.

Keywords: National Education Policy, 2020, Technical Skills, Life Skills, Holistic and Multidisciplinary Education, Multiple Entry-Exit System, Academic Bank of Credit

Research Methodology: Data for the research has been collected from secondary sources.

The Objective of Research:

1) To know the Innovative Disruption of Holistic Education and Multiple Entry-Exit System among Stakeholders Academic Bank of Credit.

2) To know the goal of NEP, 2020 to provide holistic and multidisciplinary education.

Introduction:

National Education Policy 2020 It is a major initiative with the aim of radical change in the education system from school education to higher education, flexibility, and enabling the youth to face the global challenges of the twenty-first century. The process of deliberation and discussion to prepare the National Education Policy started from the year 2015. A committee of educationists, under the leadership of former ISRO chief Prof. Kasturirangan, discussed with students, parents, teachers, researchers, social workers, and voluntary organizations from all over the country about the issues to be considered and the changes needed in the Indian education system from school education

to higher education and research. The National Education Policy has been prepared by inviting more than two lakh responses and suggestions received from the public. National Education Policy 2020 is India centric policy. Along with providing modern education to Indian youth, it will also connect with Indian culture and rituals. In this, there is an attempt to link education with 'knowledge, science, research, thought and culture'. It aims to achieve 100 percent GER by providing universal access to higher secondary education by the year 2030 and increase the GER in higher education including vocational education from 26.3 percent to 50 percent by the year 2035. The target is to increase public investment in the education sector from the current 4.43 percent to 6 percent.

The Ministry of Human Resource Development has been renamed the Ministry of Education. A central body will be formed under the Ministry of Education, which will regulate state-level education boards. In primary classes, there will be arrangements for teaching in the mother tongue or regional language for children. To ensure equal, holistic, and multidisciplinary education, there will be freedom in choosing the subject of choice. The education system will endeavor to develop scientific and rational thinking. Co-curricular like sports, vocational education, arts, commerce, and science will be there at every level. Students will have the freedom to choose the courses of their choice. It will focus on a multilingual education system, in which teaching will be done in regional languages.

The youth who want to get into the job will do a three-year bachelor's degree program. To go into research, one has to complete a four-year undergraduate degree program and a one-year postgraduate degree program. However, a four-year multidisciplinary Bachelor's program will be the preferred option and the student will be awarded a degree with accompanying project work. By the year 2040, all higher educational institutions have to be made multidisciplinary. Each will have more than three thousand students. By the year 2030, there will be at least one multidisciplinary institute in or near every district. To follow the three-language formula in schools as well as in higher education, Sanskrit will be encouraged.

New National Education Policy 2020, A Journey Toward a More Holistic and Multidisciplinary Education:

India's new education policy is the beginning of a new era for higher educational institutions. The new education policy of India, which has come after 34 years and is the first education policy of the 21st century, is a revolutionary step from the educational point of view in India. It will bring about a paradigm shift in our schools and institutions of higher learning and help India emerge as a global knowledge superpower. In the new education policy, the proposal made to allocate 6 percent of India's GDP to the education sector is unprecedented.

New Education Policy 2020 is a step towards improving the quality of research. Establishing strong research-oriented educational institutions and promoting and disseminating R&D at the level of state and national universities is an important point in the new education policy. The new education policy focuses on research and innovation through startup incubation centers, technology development centers, better coordination between industries and educational institutions, and interdisciplinary research, etc. Indian Research Foundation will promote research and innovation through funding in higher educational institutions and this step will lead to stability and rapid development of R&D in the field of education.

In the New Education Policy 2020, importance has also been given to the use of technology in education and some promising ideas such as blended learning, student-tailored curriculum, and measuring student learning progress have been included. Along with this, the new education policy also recommends continuously testing the performance of universities through evaluation and quality examination systems. The principle of internationalization of higher education is based on

the exchange of students, teachers, institutions, and programs between different countries, but in India, it has been mainly one-sided. Every year about 5 lakh students from our country go abroad for education, while for the last three years about 40,000 students mainly from South Asia and Africa are coming to our educational institutions for education from outside. Similarly, about 0.3 percent of our teachers are from an international background. The main reason for this trend is that the quality of education in international universities is better than in our universities. The new education policy will help solve all these challenges and will guide Indian higher education institutions to make them international standards.

The aim of the New Education Policy 2020 is to increase the ranking and rating and quality of education. It is a fact that rankings and ratings have become an important part of the higher education sector. And it contributes significantly to making the perception of students, teachers, parents, employers, and other authorities related to higher education. In the last decade, efforts by government and private institutions to strengthen rankings and ratings have strengthened the thought of making educational institutions world-class. International and National Accreditation Rankings and Ratings parameters, fundamentally innovative curriculum, quality teaching-learning methods, are based on the quality of teachers, skill and knowledge enhancement of students, diversity and accessibility, research and innovation, educational development and working style of ideal governance method.

All these processes of evaluation have helped educational institutions to maintain a good student-teacher ratio, continuous professional development and capacity building of teachers, and increase their international exposure through student and faculty exchange. The rankings and ratings, which are based on international evaluation standards and have been prepared to keep in mind the local realities, are helping these institutions to achieve international standards, while also providing great value to students, parents, and others. It also helps people associated with this field to understand the strong aspects and challenges of the institutions.

India has a long tradition of holistic and multidisciplinary learning from universities such as Takshashila and Nalanda, combining subjects across regions in India's extensive literature. Ancient Indian literary works such as Banabhatta's Kadambari describe a good education as having 64 knowledge of arts; And among these 64 were not just arts subjects, such as singing and painting, but 64 scientific fields, such as chemistry and mathematics, business, carpentry and clothing-making, professional fields, such as medicine and engineering, as well as communication, discussion, and Communication topics included. All branches of creative human endeavor, including mathematics, science, vocational subjects, vocational subjects, and soft skills, should be considered 'Indian arts'. This notion of 'knowledge of many arts' or what in modern times is often called 'liberal arts' should be brought back to Indian education, as this is exactly the kind of education needed for the 21st century. Will happen. The new education policy in 2020 is going to do the same thing.

A holistic and multidimensional education in the New Education Policy 2020 will aim to develop all the potential of a human being – intellectual, aesthetic, social, physical, emotional, and moral – in an integrated manner. Such education will help develop well-rounded individuals who possess significant 21st-century competence in the arts, humanities, languages, sciences, social sciences, and business, technical, and professional fields. Such a holistic education would be in the approach to all graduate programs including professional, technical, and vocational subjects. A holistic and multidisciplinary education, which has been described so beautifully in India's past, is exactly what is needed for India's education to lead the country into the 21st century and the Fourth Industrial Revolution. Even engineering institutes like IITs will move towards holistic and multidisciplinary education with more arts and humanities. Arts and Humanities students will aim to learn more science and all will try to incorporate more vocational subjects and soft skills. In this way,

the new National Education Policy 2020 is a journey towards a more holistic and multidisciplinary education.

Conclusion:

Today there is a need to emphasize the vision of Swami Vivekananda in conceiving the overall perspective of education and it is time to emphasize value-based education to the learners. Today there is a need to throw light on various aspects of holistic education and flexibility through a multi-entry-exit system. There is a need to emphasize social and emotional literacy. At present, there is also a need to focus on skills such as eagerness to learn, ability to analyze, critical thinking, and conceptual clarity in the assessment of students. Emphasis on multidisciplinary education will develop the potential of the students and they will be able to think outside of the box. There is a need today to give information about the eligibility level, credit requirement, and other aspects of the UGC rules and guidelines for the Academic Bank of Credit (ABC) and Multiple Entry-Exit System so that students will be able to choose the right career.

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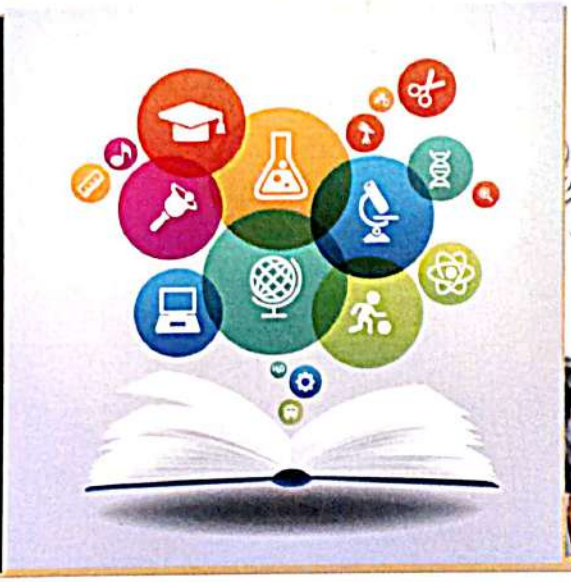
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INDEX

No.	Title of the Paper — Authors' Name	Page No.
1	Kamala Das' Poetry: Reflection of Feminine Sensibility — **Dr. Deepmala M. Patode**	1
2	A Case Study of the Impact of GST on Indian Economy — **Dr. Phole Kamal Bhaurao**	3
3	Cognitive Developments of Children and it's concepts — **Dr. Jyotsna Pusate**	8
4	Renewable Energy In India: Current Status And Future Potentials — **Dr. Patil Bhagwan Shankar**	10
5	A Study On Green Business In India — **Dr. Sou. Parvati B. Patil**	15
6	Critical Study Of Modern Appraisal System As Hr Tool With Special Reference To State Bank Of India" (Western Region) (20011-12 To 2021-22) — **Dr. Ajay Nanaji Saratkar**	19
7	Stress Management at the Workplace — **Dr. Amey Vinayak Kale**	25
8	Role of stand-up india scheme to backward class and woman empowerment. — **Dr. Raju Madan Prasad**	28
9	पावसाळ्यातील आजार व आरोग्याची काळजी — प्रा. डॉ. विद्या ठवकर	30
10	महानगरी अधोविश्व आणि स्त्रीप्रश्नांची बहुरेपीयता(भाऊ पाध्ये यांच्या कथासाहित्याच्या संदर्भात) — डॉ. शीतल पावसकर-भोसले	33
11	गाविलगड किल्ल्याचा इतिहास व त्याची शौर्य गाथा — प्रा. डॉ. गजेन्द्र बी. ढवळे	37
12	लोकशाही विकेंद्रीकरण आणि पंचायत राज — डॉ. दिनेश सहदेवराव धाकडे	41
13	जमशेदजी टाटा यांचे आर्थिक विकासात योगदान — डॉ .राजु अंबाडकर	45
14	नवीन शैक्षणिक धोरण २०२० एक अवलोकन — प्रा.तिलकचंद पी.शेंडे	47
15	स्वामी विवेकानंद के शैक्षिक एवं सामाजिक चिंतन की वर्तमान परिपेक्ष्य में सार्थकता — प्रा. शिवचरण ना. धांडे	49
16	आत्मनिर्भर भारत — डॉ.शाहेदा मुनाफ	56
17	भारतीय राजकारणात राज्यपालांची भूमिका — प्रा. सुरेंद्र हरिभाऊ किन्हिकर	61
18	धर्मनिरपेक्षता — **Dr. Umeshkumar Shahare**	64
19	आचार्य विनोबा भावे यांचे समाजविचार व कार्य — प्रा.डॉ. राजेन्द्र एम. देवाळकर	67

गाविलगड किल्ल्याचा इतिहास व त्याची शौर्य गाथा

प्रा. डॉ. गजेन्द्र बी. ढवळे
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मो. न. ९४२३६२३३२४

प्रस्तावना :

सौदर्याने नटलेल्या अत्यंत अशा दुर्गम मेळघाट मधील चिखलदरा भागात गाविलगड किल्ला आहे. तो "२१.४७ उत्तर अंक्षाशावर व पूर्वेस ७७.३३ रेखांशावर आहे. हा किल्ला अमरावती पासून ८५ कि. मी तर परतवाडा येथून मोथा मार्गे ३३ कि. मी. तर घटांग मार्गाने गेल्यास ४८ कि.मी. अतरावर चिखलदरा येथे पोहचता येते. तेथून २ कि. मी. अंतरावर प्रचंड व विशाल असा गाविलगड किल्ला दिसतो. तो इतिहासाची साक्ष देत, ऊन वारा पाऊस याचा मारा सहन करीत उभा आहे. महाराष्ट्रातच नव्हे तर भारतात मोजक्या, मोठया व अवाढव्य किल्ल्यात त्याचे नाव आहे. हा किल्ला अंत्यत मजबूत व त्याला मान्याची जागा नसल्यामूळे तो सर करणे अवघड होते. संरक्षणाच्या दृष्टीने तो प्रसिध्द होता. म्हणून तेथे यादव काळापासून तर भोसले काळापर्यत अनेक राजवशांनी येथूनच वऱ्हाड प्रांताचा कारभार केल्याचे दिसते. आणि म्हणूनच इंगजांनी गाविलगड किल्ल्यावर आक्रमण करून तो मराठयांच्या म्हणजेच नागपूरकर भोसल्याच्या ताब्यातून आपल्याकडे घेतला. आणि किल्लयावर युनियन झॅक फडकू लागला. यावरूनच हा किल्ला वऱ्हाड प्रांताकरीता महत्वपूर्ण होता. स्वतंत्र्योउत्तर काळात हा किल्ला केंद्र सरकारच्या पुरातत्व विभागाचे संरक्षित स्मारक आहे. आजपर्यत तो दुर्लक्षित होता. अलीकडेच पुरातत्व विभागाचे दुरूस्ती करण्याचे कार्य सुरू केले. विदर्भातील आपल्या तेजस्वी व स्फूर्तिदायक इतिहासाची साक्ष देते गाविलगड किल्ल्याला बराच मोठा असा इतिहास आहे. यादव काळापासून ते आधूनिक काळापर्यचा इतिहास येतो तरी या शोध निबंधाच्या माध्यमातून याचा इतिहास सांगता येईल.

गाविलगड किल्ल्याचा प्राचीन इतिहास: सर्वच दंत कथा दुर्लक्षीत करून चालत नाही तर काही दंत कथेचा अधार घेतल्यास त्याचा तर्क सुध्दा सत्य असू शकतो. म्हणून तेथील एक दंत कथा अशी की, अत्यंत महाभारत काळात या मेळघाटात वैराट राजाची राजधानी होती. तेथे वैराटगड हा किल्ला होता. राजधानी वैराट गडावर असल्याचे प्रमाण दिसून येते त्याठिकाणी जेथे चिखलदऱ्यावरून सनसेट पॉईट म्हणून ओळखल्या जाते तेथे एक टेकडी व देवीचे मंदिर आहे त्या ठिकाणी जताना एक खोल दरी असून तेथपर्यत महाल असावा कारण प्राचीन काळात अशाच दरीचा उपयोग करून पाटल्यांचा पूल तयार करीत असत. जेने करून तो शत्रू आल्यास तो वर उचलीत असत. आणि तेथून महालात येणे शक्यच नव्हते नंतर इंग्रज काळात आता पूल बांधला आहे हे ठिकाण चिखलदरा येथून १२ कि. मि. अंतरावर आहे. तेथे विराट राजचा दरबार असून गाविलगड किल्ल्यावर त्याचे सरक्षक राहत. त्या ठिकाणी त्याचा सेनापती किचक हा राहत असे.

पांडव अज्ञातवासात असताना अत्यंत दूर्गम भागातील वैराट राजाकडे नावे बदलून नोकरी करीत होते. असे पूरानातील कथेत दिसते ऐके दिवशी किचकाने द्रौपदीचा हात पकडला. ही गोष्ट द्रौपदीने भीम यास सांगितली. म्हणून भीम संतापला व त्याने किचकास मल्लयुध्दाकरीता आवहान दिले. त्यावेळी दोघांमध्ये तुंबळ युध्द झाले. त्यात भीमाने किचकाचा वध करून ज्या दरीत टाकले त्या दरील किचकदरी म्हणून प्रसिध्द झाली. हा इतिहास खरा मानला तर गाविलगड त्याला पूर्वी गवळीगड असे म्हणत. कारण तेथे पूर्वीपासून गवळी लोक राहत असत आजही मोठया प्रमाणात गवळी लोंकाची वस्ती आहे. त्यांना पूढे यादवराजाचे सरंक्षण लाभत असे व त्यांची गुरे ढोरे जंगली जनावरापासून सुरक्षित ठेवण्याकरीता या किल्ल्याचा उपयोग होत असे. यावरून गाविलगड किल्लयाचे मूळ बांधकाम देवगिरीचे यादव यांचा अचलपूरचा मांडलिक राजा दरण्णाच्या काळत करण्यात आले असावे.[1] त्याकाळी हा भाग त्याच्या राज्यात मोडत होता. म्हणून या भागास गाविल सरकार संबोधल्या जात असे आणि त्याचे सरंक्षण करण्याकरिता तेथे मातीचा किल्ला बाधल्याचा उल्लेख आढळतो.

मध्ययुगीन इतिहासात गाविलगड किल्ल्याचे महत्व:

इ. स. १४ व्या शतकात दिल्ली सुलतान फिराजशहाच्या काळात इस्माईल मख याने बंडाळी करून सर्व मुस्लीम अधिकारी आपलेकडे वळविले सर्व सुत्र हसन जाफर गंगु बहामनी यास दिले.[2] हाच दक्षिण भारतात सुलतान बनला. त्यावेळी त्याच्या ताब्यात वऱ्हाड प्रांत व गाविलगड, नरनाळा व मेळघाटातील लाहान मोठे किल्ले जसे भैरवगड बवरगड असे डोगरी किल्ले ताब्यात होते. तेव्हा वऱ्हाड प्रांत हा स्वतंत्र सुभा होता. त्यावेळी खेरल्याचा राजा नरसिंगदेव राय हा वारंवार हिंदू सत्ता प्रस्तापित करण्याचा प्रयत्न करीत असे त्याचा बदोबस्त करण्याकरीता बहामनी साम्राजाचा नववा सुलतान महम्मदशहा वली याने अचलपूरच्या किल्लयात इ. स. १४२५ मध्ये राहून खान–ए–आजम अब्दूल लतीफ या अधिकाऱ्या कडून गाविलगड किल्ल्याची दुस्ती करवून घेतली.

बहामनी साम्राज्याचे पाच तुकडे पडले त्यात प्रथम फतेउल्ला इमाद उल मुल्क याने अचलपूर ही राजधानी ठेऊन वऱ्हाड प्रांत स्वतंत्र राज्य घोषित केले. त्यावेळी त्यावेळी त्यावेवर बहामनी सुलतान व बारीदशहा यांनी विजापूर वऱ्हाडवर आक्रमन केले तेव्हा इमादशहा हा गाविलगडावर राहिला त्याच्या मदतीस विजापूरचा आदिलशहाही आपल्या सुरक्षितते करीता गाविलगडावर होता. व त्याने तेथूनच दोन्ही सुलतानाला परत जावे लागले.[3] संरक्षणाच्या दृष्टीने हा किल्ला किती महत्वाचा आहे हे त्याला समजले व त्याने गाविलगड व नरनाळा किल्ल्याची दुरूस्ती करून आपले संरक्षणाचे ठाणे बनविले. मेळघाटातील सर्व किल्ले आपल्या ताब्यात घेतले. फतेउल्ला इमादउलमुल्क नंतर अहमदनगरच्या मुर्तजा निजामशहाने वऱ्हाडवर आक्रमण केले तेव्हा अखेरचा अचलपूरचा सुलतान तुफालखान व त्याचा मुलगा हे सुरक्षित राहण्याकरीता गाविलगड किल्ल्यात राहीला.[4] त्यानंतर गाविलगड किल्ला निजामशाहीत आला. मोगल बादशहा अकबराने वऱ्हाडवर आक्रमण करनार ही गुप्त वार्ता मेताच निजामशहाने ऐलिचपूरचा सुभेदार सय्यद मुर्तिजा सब्जावरी याला हुकूम केला की, उत्तरेची सिमेचा बदोबस्त करावा म्हणून त्याने गाविलगडावर प्रचंड पैसा खर्च केला. तेथील किल्लेदार बहिरामखानाने किल्ल्याची बक्कम दुरूस्ती करून घेतली. व एका प्रचंड असा बुरूज बांधला त्यावर आपले नाव कोरले आहे ते अद्यापही कायम आहे. त्याचा हिजरी सन ९८५ लिहीला आहे.[5] इ.स. १५७७ निजामशाहीनंतर गाविलगड किल्ला मोगलांच्या ताब्यात आला. त्यावेळी अकबराच्या नवरत्न दरबारातील अबुल फजल वऱ्हाडात राहिला त्याने असे वर्णन केले की वऱ्हाडात लोखंडाच्या खानी असून गाविलगडावर पोलादी शस्त्रांचे काम चांगले होत असे.[6] औरंगजेबाच्या मृत्यू नंतर मराठा साम्राज्य निर्माण झाले.

राजारामाच्या कारकिर्दित परसोजी भोसले यांनी स्वबळावर गोंडवना व वऱ्हाड प्रांतावर आपले शसन बसविले. राजारामाने त्याला 'सेनासाहेब सुभा' हा किताब दिला होता. आणि हा प्रदेश परसोजी भोसले यांना दिला. इ. स. १७१८ मध्ये कान्होजी भोसले यांना वऱ्हाडातून चौथाई व सरदेशमुखी वसुलीचे अधिकार मिळाले. कान्होजी नंतर रघूजी भोसले यांने वऱ्हाडात मराठयांची सत्ता बरीच वाढविली व सुव्यवस्थित राज्यव्यवस्था राबविली इ. स. १७३८ मध्ये ऐलिचपूरचा सुभेदार शुजातखानाचा पराभव करून गाविलगड व नरनाळा हे दोन्ही मजबूत किल्ले आपल्या ताब्यात घेतले.[7] नंतर काही काळ तो निजामाच्या ताब्यात होता. शके १६७४ इ.स. १७५२ मध्ये रघूनी भोसले यांनी पहिल्या राणीचा पूत्र चंद्रपूरचा सेनाधुरंधर मुधोजी भोसले यास गाविलगड किल्ला जिंकण्यास पाठविले तेव्हा त्याने प्रचंड पराक्रम करून गाविलगड सर केला. इ.स. १७५५ ला वऱ्हाडातच रघूजी भोसले यांचा मृत्यू झाला. त्यावेळी मुधोजी गाविलगड किल्ल्याचा बदोबस्त करून नागपूरकडे निघण्याच्या तयारीत होता. तेव्हा त्याने रघूजी भोसले यांचा क्रियाकर्म अंजनगाव सूर्जी येथे आटपून पहित्या राणीचा पूत्र म्हणून कर्तव्य केले. रघूजीच्या मृत्यू नंतर मुधोजी भोसले गाविलगडास राहीले.[8] व त्यांच्याही सरक्षणाचे ठाणे गाविलगड किल्ला हेच होते. नंतर भोसल्यांनी हैद्राबादच्या निजामाचा पराभव करून त्याच्या कडून साठ चाळीसीचा तह केला.[9] व साठ टक्के वसूल भोसले करीत. नागपूरकर भोसले यांनी या किल्ल्याचा बाहेरचा परकोट बांधून पूर्ण केला.

आधुनिक काळातील गाविलगडचा इतिहास:

भोसल्यां तर्फे गाविलगडच्या किल्ल्यावर जानोजीच्या पक्षातील जयाजीभाई यास गाविलगड किल्ल्याचा किल्लेदार नेमले.[10] इंग्रजाच्या काळात भोसल्यांनी बेनिसिग नावाचा शूर राजपूत अधिकारी होता. त्यालाच किल्लेदार समजत. बेनिसिंगाचा मूळ पुरूष झामसिंग होता. त्याला रघूजी भोसले यांनी बंगालातून पाडाव करून आणले होते. परंतु त्याचा पराक्रम पाहून झामसिंगास मेळघाटातील सर्व किल्ले ताब्यात देऊन सर्व किल्लेदारंचा अधिकारी नेमले होते. त्यानंतर त्याचा पुतण्या प्रगोदसिंग व नंतर दर्यावसिंग व नंतर बेनिसिंग गाविलगड किल्ल्यात राहत असत. गाविलगडाच्या रक्षणासाठी अनेक मराठे व राजपूत सैन्य गाविलगडावर राहत असत.

इंग्रज मराठा संघर्ष १४,१५, डिसेंबर १८०३:

इ.स. १८०३ च्या दुसऱ्या इंग्रज–मराठा युध्दाच्या वेळी भोसले आणि शिंदे यांनी वऱ्हाडात धुमाकुळ घातला होता. त्यांचा बदोबस्त करण्याकरीता इंग्रज अधिकारी वेलस्ली वऱ्हाडवर चालून आला. त्यावेळी अचलपूरचा नबाब सलाबतख हा होता.[11] निजामाने इंग्रजांशी पुर्वीच तह केलेला असल्यामुळे 'सबसीडियरी सिस्टिमच्या' कलमाप्रमाणे ठेवलेली आपली फौज इंग्रजांच्या मदतीस दिली. व राजा गहिपतराम व नबाब सलाबतखां यांना इंग्रजांना मदत करण्याचा हुकूम केला.[12] त्याप्रमाणे सलाबतखां वेलस्लिच्या सैन्याला अडगांवच्या लढाईत येऊन मिळाला. अडगावच्या लढाईत घनघोर युध्द झाले. मराठयांचा मराठयांना मापार घेणे भाग पडले. तेथे मराठयांचा तोफा व दारूगोडा हो इंग्रजाच्या हाती लागला याचाच उपयोग त्यांनी गाविलगडाच्या वेढयासाठी केला. अडगावच्या लढाई नंतर हे सर्व लष्कर एलिचपूरहून गाविलगडचा किल्ला घेण्यास निघाले.

वेलस्ली दिनांक ५ डिसेंबर १८०३ मध्ये एलिचपूरास आला व दिनांक ७ रोजी किल्ल्याच्या पायथ्याशी देवगाव येथे येऊन पोहचला व आपला दुसरा अधिकारी स्टिव्हनसन याने बऱ्हाणपूर विजित करून तो मेळघाटातून वेलस्लीस येऊन मिळाला. यास उत्तरेकडून हल्ला करण्याकरिता पाठविले या प्रदेशाची माहिती ऐलिचपूरच्या नबाब सलाबतखांच्या पदरी बरेच मेळघाटातील सैन्य होते त्यापैकी एका जाणकाराच्या सांगण्यावरून वेलस्लीला एका टेकडीवरून मारा करता येईल सांगितले म्हणून ३० मैलाचा फेरा घेऊ स्टिव्हनसन उत्तरेकडील बाजूस किल्ल्याजवळील लवादा या गावात जाऊन पोहचला. त्याने

दिनांक १२ च्या रात्री उत्तर दरवाजावर मारा करण्याकरिता तोफखाना लावून ठेवला.[११] तर वेलस्लीने त्याच रात्री दक्षिणेकडील फिरफत्ते दरवाजावर मारा करण्याची सर्व तयारी केली होती.

१३ तारखेला सकाळपासून दोन्ही कडून तोफांचा मारा सुरू झाला. वेलस्लीकडून विशेष मारा झाला नाही कारण मोठया तोफा वर चढविता येत नव्हत्या त्यामुळे किल्ल्यावर मारा होईना वेलस्लीने पितळी लहान तोफांचा उपयोग केला परंतु त्याचा फार उपयोग झाला नाही. मात्र किल्ल्यातील लोकाचे लक्ष मात्र विचलीत झाले. परिणामी स्टिव्हनसन यास मदत होऊन त्याने उत्तरेकडील मारा सुरू ठवला. १४ तारखेला सायंकाळी किल्ल्यास भगदाडे पडली. त्यातून हल्ला करण्याची तयारी रात्रभर सूरू ठेवली. केनी नावाच्या इंग्रज अधिकाऱ्यास हाताखाली मद्रासचे हिंदी पायदळ व स्टिव्हनसनचे हिंदी लष्कर व काही इंग्रज पलटणी देऊन १५ तारखेला दिवसा १० वाजता हल्ल्यास उत्तरेकडून सुरूवात केली. इग्रज सैन्य भगदाड पडलेल्या तटबंदीतून आत धुसू लागले.[१४] व हातघाईच्या लढाईस प्रारंभ झाला. त्यावेळी मराठे व राजपूत सैन्याने प्रचंड पराक्रम गाजविला अनेक इंग्रज सैन्याला जेरीस आणले. व उत्तरेकडील केनीचे आक्रमण काही काळ थोपवून धरले.

इकडे दक्षिणेकडे वेलस्लीने आपल्या सैन्याच्या दोन तुकडया तयार केल्या आपण स्वत: दक्षिण दरवाज्यावर राहिला कॅप्टन चार्मस यास वायव्येकडील दरवाज्यावर पाठविले. या दोन्ही तुकडयांची काहीच डाळ शिजेना दरवाजा काही पडेना. किल्ल्यातील सर्व सैन्य उत्तर दरवाज्यावर जाऊन पडले असते परंतु वेस्लीच्या दक्षिणेकडील माऱ्यामुळे किल्यातील सैन्याची शक्ती विभागल्या गेली. उत्तरेकडे मात्र केनीच्या नेतृत्वात असलेल्या इग्रज सैन्यास मदत झाली. किल्ल्यावरील सैन्य हटवून वायव्यकडील दरवाजाने बाहेर पडत होते. व दरवाजा आयताच उघडल्यामुळे चार्मस यास सहज किल्ल्यात प्रवेश झाला. प्रथम त्याला यश मिळाले परंतु किल्ल्यातील राजपूत व मराठे निकराने लढले. व आणखीन थोडया तग धरते तर कदाचित केनीचा पराभव निश्चित होता. केनीने एक तुकडी वायव्यकडील खूनी दरवाजावर पाठविल्याने चार्मस याने पळणाऱ्या लोकांची कत्तल करून आतील सैन्यास मदत केली. इंग्रजानी फक्त अर्धेच कार्य पूर्ण केले. गाविलगड किल्ल्यात दोन तंटबंदी असून एक आतिल किल्ला व दुसरा बाहेरचा किल्ला असा दुहेरी बंदोबस्त होता. बाहेरचा किल्ला इंग्रजांच्या ताब्यात आला असला तरी आंतील किल्ला मजबूत असल्याने तोफाही काम करीत नव्हत्या तर दिल्ली दरवाजा हा मजबूत असल्याने उघडत नव्हता तेथे किल्लेदार बेनिसिंगाने बदोबस्त चोख ठेवला व स्वत: जातीने उपस्थित होता. त्यावेळी कॅप्टन कॅपबेल जो एक लहान ९४ बटालीयनचा नेता होता त्याचे सैन्य आतला किल्ला घेण्याच्या तयारी करीत होत.[१५] इंग्रजाना किल्ल्यावर चढून जाण्याशिवाय मार्ग नव्हता म्हणून शिडया लावून इग्रज लष्कर वर चढले. त्यावेळी अनेक इंग्रज सैनिक धाराशाई होऊ लागले. परंतु अखेर त्यांनी किल्ल्यातील भिंत पार केली, व हल्ला करून दरवाजा उघडला. बाहेरील किल्ल्याच्या रक्षणार्थ अनेक मराठे व राजपूत सैन्य होते. तेथे प्रचंड संघर्ष केला हातघाईची लढाई बरेच वेळ चालली शेवटी कल्ल्यातील सैन्य भोसल्यांचे सैन्य धाराशाही होऊ लागले. ते पाहून काही सैन्य पळून गेले. शूर इमानी बेनिसिंग व त्याचे सोबत चे राजपूत सैन्य मात्र अखेरपर्यंत गंडबेरूड दरव्याज्याजवळ अखेरच्या श्वासा पर्यंत लढले. दरवाजा उघडला तेव्हा प्रेतांचा खच पडला होता तर तेथेच किल्लेदार बेनिसिंगाचे प्रेत दरवाज्या जवळ सापडले. त्याचा पराक्रमामुळे व मराठयांचा चिवटपनामुळेच गाविलगड अजरामर ठरला.

प्रचंड इग्रज सैन्यापुढे आपला टिकाव लागत नाही हे पाहून किल्ल्यातील स्त्रियांनी जौहर केला. जौहर व्यवस्थित न झाल्याने बारा पैकी दोनच स्त्रिया अग्नीत समर्पित झाल्या. इंग्रजाना गाविलगड किल्ल्यात बरीच लूट सापडली. त्यापैकी बरीच लुट नबाब सलाबतखानाने उंट व घोडयावर लादून एलिचपूरास आणली. यात भोसल्याचा खजिना व बहुमोल कुराणाची प्रत सापडली ती ऐलिचपूरच्या नबाबाने नेली. गाविलगडच्या युध्दानंतर सलाबतखान व वेलस्ली ऐलिचपूरास आला. वेलस्लीचे जखमी इंग्रज सैन्य बरे होईपर्यंत तेथेच मुक्कामास होते. त्यापैकी कर्नल केनी या युध्दात मारल्या गेला. त्याची कबर सरकारी दवाखाण्याच्या पाठीमागे आहेत. त्या मी स्व:ता पाहिल्या आहेत. दोन दिवसांनी १७ तारखेला डिसेंबर १८०३ रोजी इग्रज व भोसले यांच्या तह झाला तोच 'देवगांवचा तह' या नावाने प्रसिध्द आहे. यात कटक, बलसोर हे प्रांत व वर्धा नदीच्या पश्चिमेकडी वऱ्हाडचा सर्व प्रदेश भोसल्यानी इंग्रज व त्यांच्या साथीदार यास द्यावा व गाविलगड व नरनाळा हे किल्ले व त्याखालचा प्रदेश भोसल्यांकडे ठेवावा असे ठरले.[१६] अशा प्रकारे गाविलगड किल्ल्याची शौर्याची व पराक्रमाची, इतिहासात अमर राहील अशी गौरव गाथा आहे.

त्यानंतर आप्पासाहेब भोसले व इंग्रज यांच्यात इ.स. १८१८ मध्ये झालेल्या तहाने गाविलगड व नरनाळा हे किल्ले इंग्रजांच्या ताब्यात देण्याचे ठरले. त्याप्रमाणे इ. स. १८२२ मध्ये या दोन्ही किल्ल्यावर ईस्ट इंडिया कंपनीचा ध्वज फडकू लागला. आणि गाविलगड किल्ला पारंतत्रात अडकला.

निष्कर्ष : गाविलगड किल्ल्याला प्रचंड असा इतिहास आहे. अनेक जून्या साहित्यात व यादवकाळापर्यंत या किल्ल्याचे महत्व होते. त्यानंतर मध्ययुगीन काळातर त्याला प्रचंड महत्व प्राप्त झाले होते. कारण बहामनी सुलतानाच्या काळात या ठिकाणीच त्याचे सुभेदार बैठका घेत असत व आपली रणनिती तयार करीत. ज्यावेळी बहामनी साम्राज्याचे विघटन झाले तेव्हा ऐलिचपूरचा सुभेदार फत्तेउल्ला इमाद उल मुल्क याने बहामनी सुलतानापासून बाहेर निघुन स्वतंत्र राज्य स्थापण केले तेव्हा

बरीदशहा व युसूफ आदिलशहा यांनी सुध्दा त्याचा फायदा घेतला व स्वंतत्र झाले. जेव्हा बहामनी सुलतान यांचे ह मोडण्याकरीता आला तेव्हा सर्व सुलतानांनी गाविलगड किल्ल्यावर आश्रय घेतला होता. तसेच आधुनिक काळात हा किल्ल नागपूरकर भोसले यांच्या कडे असताना इंग्रज मराठा युध्दात सिंधे आणि भोसले एक झाल्यास इंग्रजाना भारी जाईल म्ह मराठयांमध्ये फूट पाडून या इंग्रजांनी हा किल्ला घेतला व भोसले यांच्या सोबत देवगावचा तह केला. तरीही भोसल्यांनी किल्ला आपल्याा ताब्यात ठेवला. पुढे इंग्रजांच्या ताब्यात गेला. यावरून निष्कर्ष निघतो की हा किल्ला राजकीय दृष्ट महत्वाचा होता.

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९. नागपूरकर भोसल्यांची बखर पान ५३ व ७४.
१०. काळे या. मा., उपरोक्त, पृ.क्र. ३८१.
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१३. कित्ता, पृ.क्र. २०७.
१४. महाराष्ट्र स्टेट गॅझिटीअर, अमरावती डिस्ट्रीक्ट, मुंबई १९११, गॅझिटीयर ११०.
१५. काळे या. मा., उपरोक्त २११
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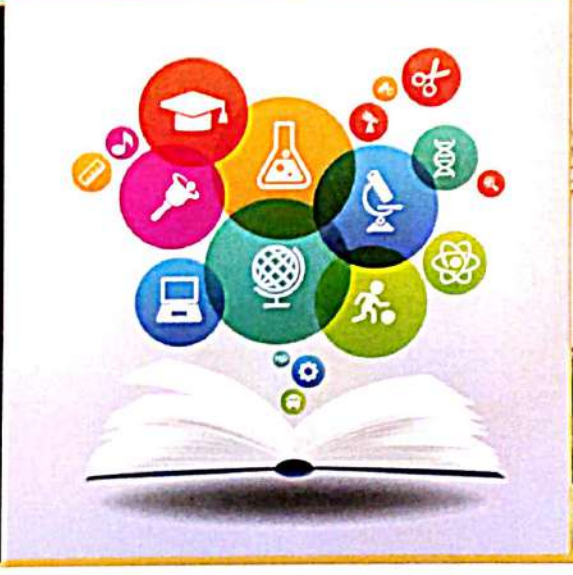
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INDEX

No.	Title of the Paper — Authors' Name	Page No.
1	The Feminist in the International Relations — **Ravina Kumari**	1
2	Comparative Study Of Strength And Power Of Hammer Throw And Shot Put Players — **Dr.Virendra R Talreja**	5
3	A Case Study of Advantages and Disadvantages of GlobalisationFrom the Industrial Perspective — **Dr. Phole Kamal Bhaurao**	9
4	Application of Artificial Intelligence on Behavioral Finance — **Dr. Sou. Parvati B. Patil**	13
5	Economic Impacts of Artificial Intelligence — **Dr. Patil Bhagwan Shankar**	17
6	The Indian Feminist Classic Dr. B. R. Ambedkar — **Dr.Subhash G. Raut**	21
7	Post Activation Potentiation And Its Practical Application In Contrast Training: A Brief Review — **Aparna Rathi1, Dr. Deepak Sharma2**	24
8	राजनीतिक दल : लोकतांत्रिक व्यवस्था में राजनीतिक दल की भूमिका — अंजू व्यास	28
9	संत साहित्यातील मानव कल्याण विचार — डॉ. विवेक देशमुख	32
10	भारतीय निवडणूक प्रक्रियेतील एक महत्वपूर्ण सुधारणा 'नोटा' — कु. स्वाती युगेंद्र अंबळकार ,डॉ.संगिता भांगडीया (मालाणी)	35
11	मोगल कालीन स्त्रियांची सामाजिक स्थिती — प्रा.डॉ. कैलास आर. भांडारकर	40
12	नविन शिक्षण धोरण २०२० : स्वरूप आणि आव्हान — डॉ.पंकज पुं. कावरे	46
13	राष्ट्रसंत तुकडोजी महाराज यांच्या सामुदायिक प्रार्थनेची आजच्या पिढीला गरज आणि महत्व — प्रा.संजयकुमार सिताराम राठोड,डॉ. अमोल मांडेकर	52
14	ब्रिटीश कालखंडातील शेतकरी आंदोलन — प्रा.डॉ. बोचरे जे. एम.	56
15	इमादशाही कालीन वऱ्हाडातील हिंदू लोकांचे सण — डॉ. गजेन्द्र बी. ढवळे	59
16	'युनिफॉर्म सिव्हील कोड ' (UCC) : हिंदू कोड बिल, मुस्लिम पर्सनल लॉ, आदिवासी जनजाती कायदे — प्रा. डॉ. प्रदीप पंजाबराव दंदे	63
17	महाराष्ट्र राज्याचे बदलते राजकारण व शासन — प्रा. डॉ. विश्वनाथ आत्माराम दरेकार	71
18	साहित्य आकादेमी पुरस्कृत 'झाडाझडती,' राघववेळ; बारोमास' कादंबऱ्यांतील शेतकरी कामगारांच्या समस्या — प्रा. सतीश स. कर्णासे	76
19	संतांची ग्रंथ संपदा व मानव विकास विचार — प्रा. रविंद्र डाखोरे	81

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डॉ. गजेन्द्र बी. ढवळे
इतिहास विभाग प्रमुख कला, विज्ञान व वाणिज्य महाविद्यालय,चिखलदरा, जि. अमरावती (महाराष्ट्र)मो. न. ९४२३६२३३२४

प्रस्तावना : अचलपूर अती प्राचीनकाळपासून तर मध्ययुगापर्यंत ऐतिहासिक दृष्टया प्रसिध्द आहे. प्राचीनकाळात अच्चलपूर, महानुभाव साहित्यात अळजपूर, तर इमादशाही काळात इलिचपूर असे नाव पडले बहामनी सम्राज्याचे तुकडे झाले तेव्हा वऱ्हाड प्रांतात फत्तेउल्ला इमादउलमुल्क या पुर्वाश्रमीच्या हिन्दू पुरूष असून तो बहामनी साम्राज्यात फत्तेउल्ला या नावाने प्रसिध्दिस आला. त्याने आपल्या पराक्रमाने अचलपूर ही आपली राजधानी बनवून वऱ्हाडात स्वंतत्र राज्य स्थापन केले. त्यावेळी वऱ्हाडात सुभत्ता नांदत असली तरी शेतकरी जीवन हे अंत्यत कष्टाचे होते यात संशय राहत नाही. या कामकरी कष्टकरी लोकांना सण–उत्सवाने तेवढाच विरंगुळा मिळविण्यासाठी तथापि केवळ मनोरंजनासाठी सण–उत्सव साजरे केले जात नव्हते तर त्यामागे त्यांची नितांत धार्मिक श्रद्धा आपल्याला दिसून येते. त्याकाळी अकबरनेही गख्खी, दिवाळी, दसरा, वसंतपंचमी इ. हिंदूंचे उत्सव तो मोठया प्रमाणावर साजरा करीत असे. यावरून वऱ्हाडात हे सण मोठयाप्रमाणावर साजरे होत.

१) पोळा :–

श्रावणातल्या अमावस्येला पिठोरी अमावस्या म्हणतात, त्या दिवशी पोळयाचा सण असतो. वऱ्हाडातील शेतकरी गायीचा सण म्हणून दिवाळी तर बैलांचा सण म्हणून पोळा हा सण साजरा करीत. हे दोन सण त्यांच्या दृष्टीने फार मोठे व महत्त्वाचे समजल्या जात. आणि म्हणूनच संपूर्ण वऱ्हाडात हा सण फार धूमधडाक्यात साजरा करीत असत. पोळयाच्या निमित्याने बैलाची कामे बंद ठेवली जात असे. बैलाना ढेप, सरकी चारतात. सकाळी शेतकरी बैलाला नदीवर नेऊन पोहणी देत.[१] बैलांना घरी आणून त्यांच्या अंगावर पेला व पंजा चे गेरवाचे किंवा रंगाचे छापे मारून रंगवित. त्यांच्या शिंगांना बारनीस लावून व चमचमणारे बेगड लावित.

तोळे, माळा, फूलांचा हार व कपाळवर मठाठया बांधून अंगावर झूल चढवून सजवीत असत. आंब्याच्या तोरणाखाली बैल उभे करून पोळयांची गिते गातात. गावप्रमुखाचे बैल बुजवूण सर्वात पुढे ठेवत तो त्यांचा परंपरागत मान असे.[२] त्यानंतर पोळा सुटे व बैलांना मारूतीच्या मंदिरात दर्शनास नेवून नंतर घरोघरी पूजेसाठी बैल गावात फिरविल्या जात.[३] बहिन आपल्या भावाच्या पाठीवर काकडी फोडत असे. अशा प्रकारे पोळा हा सण हिंदू चा लोकप्रिय सण इमादशाही काळात वऱ्हाडात मोठया उत्सवात खेडया पासून तर नगरात साजरा होत असल्याचे स्पष्ट होते.

२) मारबत :–

गावातील किंवा नगरातील वाईट गोष्टी घेऊन जाण्यासाठी मारबत प्रतिकात्मक रूपात ती गावभर मिरवीली जात असे. काळी, पिवळी मारबत असे तिचे प्रकार होते. कंबरेला लाकडी उखळ, हातात मुसळ, मुसळाला घुंगरू अशा अवतारातल्या बडग्या काढून गाणे गात. काही गीते लक्षात ठेवण्यासारखी आहेत. "अगास गडगडे शिमग्यात पडले खळे तुही माय गंधण बळे तुहा बाप शिवते जोडे" अशा गितांनी मारबतीची मिरणून भल्या पहाटे निघत असे. घरातील कचरा बाहेर फेकण्याच्या निमित्ताने ओरडत असत. "माशा गोमाशा घेऊन जायवो मारबत। माश्या मुरकुटया घेऊन जागे मारबत । रोगराई घेऊन जायवो मारबत" अशा आरोडया मारत असत.मारबत रोगराई घेऊन जाते अशी वऱ्हाडी लोकांची श्रद्धा होती.

३) नागपंचमी :–

नागपंचमी हा सण वऱ्हाडात पूर्वीपासून चालू होती व आजही हा सण साजरा होताना दिसतो. भिंतीवर हळदीने, चंदनाने नागाच्या आकृती पाची बोटांनी उमटवितात. त्याची पुजा अत्यंत भक्तिभावाने केली जाते.[४] व त्याला हळदीच्या दाऱ्याची माळ घालून पूजा करीत व लाहया फुटाणे वाटून घरभर फेकीत असे. नागपंचमील पाच दिवस भजने म्हणत असत. त्यांचा पाचव्या दिवशी नदीवर शिरविण्याकरीता सर्व भक्त मंडळी एकत्र येत व नागपंचमीची पूजा नदीवर शिरविल्या नंतर सर्व भक्त गण भोजन करून आपला प्रसाद ग्रहण करीत.

४) नवचंडी :–

नवचंडी[५] म्हणजेच नवरात्र उत्सव म्हणून आज प्रचलित आहे. सणाचे व्रत आश्विनमासी शुद्ध पक्षांत येत असे. आजही आमचे कडे चालू आहे यात व्रतासाठी घट मांडून त्यावर दिवा नऊ दिवस पेटता ठेवतात. घटाखाली टाकलेल्या काळया मातीस कस्तूरी म्हणतात. त्यात नवधान्ये पेरीत. त्यावर फुलोरा म्हणजे कानोला पापडी बांधीत आणि माळ लावीत. शेवटच्या दिवशी पूर्वी बकऱ्याचा बळी दिला जात असे परंतु आता मात्र त्याचे प्रमाण नगण्या आहे. ज्या घराण्यात मांस चालत नाही अशा ठीकाणी नऊ कुमारिकेला पंचपकवाण्याचे भोजन घालीत असत.[७]

५) दसरा :–

हिंदूचा एक सण व शुभ दिवस अश्विन शुद्ध दशमीला विजयादशमी किंवा वऱ्हाडात यालाच दसरा म्हणतात.[८] या दिवशी शुंभ निशुंभ, रक्तबिज, महिषासुर या राक्षसाना मारण्यासाठी दुर्गेने चंडीचा अवतार घेऊन युद्ध केले ते नऊ दिवस चालले. आणि दशमीला महिषासुराचा वध करून अंतिम विजय संपादन केला.[९] महाराष्ट्रात या दिवशी सीमोल्लंघन करून सरदार व सैनीक घरातील शस्त्राअस्त्राची पूजा करीत ही परंपरा प्राचीन काळापासून तर आजपर्यंत चालू असलेली दिसून येते. तर शेतकरी औतांची, शेतीच्या सर्व अवजारांची पुजा करीत. अशाप्रमारे ज्यांचे जे व्यससाय असत त्या सर्व वस्तुची पुजा केल्या जात असे. त्यानंतर घरात पूरण पोळी करून नवमीच्या देवीला नैवद्य अर्पण केल्या जाई.[१०] सायंकाळी राम–रावणाचे युध्दाचे नाटक होत असे. रावण दहण करून शम्मीचे (आपटयाची) पाने 'सोने' म्हणून वडिलधाऱ्या मंडळीला घरोघरी जाऊन वाहत असत. ऐतिहासिक काळात म्हणजेच इमादशाही काळात दसऱ्याच्या दिवशी हेला वेशीत मारतात, त्यावेळी प्रथम गावचा पाटलाला त्याचा मान होता. त्यानें तलवारीचा हात मारणें म्हणत.[११] तशेच मराठा सरदार युद्ध मोहिमेवर निघत.[१२] जोशी हा सण आजही मोठया उत्साहने साजरा होतो. याशिवाय श्रावणी,[१३] पोवती, संक्रांत, आठवी, नागदिवाळी, अखजी, आखाडी, काजडती, महालक्ष्मी पूजन, माळी, वऱ्हाडात इमादशाही काळापासून आजपर्यंत साजरे होताना दिसतात.[१४]

६) दिवाळी :–

दिवाळी हा सण आनंदोत्सव म्हणून साजरा केल्या जात असे. गायीचा सण म्हणून प्रसिद्ध आहे. गुराख्याची गाणी यावेळी सर्वत्र ऐकू येत होती. गहूला (गायीची) बारस ही तर त्याच्यात प्रशिद्ध होती. दिवाळीत गायीच्या शेणाचे काती म्हणजे कुंती व महिषासुर करीत असत.[१५] आजही करतात. "चक्रधर स्वमीनी माहादाइसाकरवी दिवाळीचा सण साजरा केला होता. किकसा (संगथी पावडर)लावून अभ्यंगस्नान करून ओवाळणी केली होती."[१६] दिवाळीच्या दिवशी घरादाराची रंगरंगोटी करून घर सजविल्या जात असे. सायंकाळी रांगोळी घालून दिव्याच्या पनत्या सर्वत्र लावणे महत्वाचे असे. दिवाळीच्या पाचही दिवसाचे महात्म सांगणाऱ्या अनेक कथापूराणात आलेल्या आहे. त्याचे वर्णन थोडक्यात पूढे दिले आहे.

आश्विन वद्य त्रयोदशीला धनत्रयोदशी हे नाव आहे यमाने आपल्या दूताला दीपदान करून अमरत्व दिले अशी कथा आहे. या दिवशीपासून अभ्यंगस्नान व ओवाळून पुजा करीत. असे दिवाळीच्या पाचही दिवशी करीत. दुसऱ्या दिवशी अक्षय वद्य चतुर्दशीस नरकचतुर्दशी हे नाव आहे. या दिवशी कृष्णाने नरकासुराचा वध करून त्याच्या बंदीवासात असलेल्या १६ हजार स्त्रियांना मुक्त केले होते. तिसऱ्या दिवशी अश्वीन वद्य अमावशेला रात्री लक्ष्मीपुजन असते. अष्टदल कमळावर लक्ष्मीची स्थापना करून लक्ष्मीपुजन ऐपतीप्रमाणे थाटात करण्याची पूर्वापार परंपरा वऱ्हाडात आहे.[१७]

घरातील धनाचे व पैशाची पूजा मोठया भक्तीभावाने करून महालक्ष्मीची आरती म्हटल्या जात असे. लक्ष्मी हे सौदर्याचे, प्रेमाचे व वैभवाचे प्रतीक समजतात. चौथ्या दिवशी कार्तिक शुद्ध प्रतिपदेस 'बलीप्रतिपक्ष' हे नाव आहे.[१८] या दिवशी बळीराजास विष्णूने वामन अवतार घेऊन पाताळात लोटले व दीपदान करील त्याला नरकात यमयातना भोगाव्या लागणार नाही असा वर दिला. या दिवशी बळीपूजा करतात. शेणाचा राजा बळी बनविल्या जात असे. शेतकरी गाई–म्हशीना गेरूने व विविध रंगाने रंगवून पूजा करीत.[१९] हिंदूच्या साळेतीन मुर्हूतांपैकी हा अर्धा मूहर्त आहे. या दिवशी पत्नीने पतीला ओवाळण्याची पद्धत आहे.[२०]

पाचव्या दिवशी कार्तिक शुद्ध द्वितीयस भाऊबिज म्हणतात. महाराष्ट्रातील भाऊबहिनीचा महत्त्वाचा, आनंदाचा व मायेचा दिवस वऱ्हाडातही मोठ्या मायेने साजरा करण्याची चाल घरोघरी होती आजही आहे. लिळाचरित्रात एल्हाइसास भाऊबीज करून चक्रधरास लाडू दिले होते.[२१] दिवाळीच्या पाचही दिवस फटाके उडवून पूजेचा समारोप केल्या जात असे. या सणाला काणोले, पापडया, व विविध पदार्थचा उल्लेख लीळाचरित्रात आलेला आहे. लाडू, चकल्या, चिवडा हे पदार्थ आप्तलोकांना व मित्राना या फराळाचे निमंत्रण दिल्या जात असे.[२२] दिवाळीच्या सणामुळे वऱ्हाडातील ही परंपरा महाराष्ट्राला देणगी दिली आहे. आज महाराष्ट्र संस्कृती म्हणून आज टिकवून ठेवण्याचे कार्य होत आहे. असे नमूद करावेसे वाटते.

७) गोकुळाअष्टमी :–

यादवकाळापासून तर आजपर्यंत वऱ्हाडात हे व्रत लोकप्रिय आहे. यासंबधी लीळाचरित्रातील बोनेबाई नावाच्या एका शिष्येने गोकुळाष्टमीच्या दिवशी मातीचे गोकुळ केले. तेव्हा चक्रधरस्वामीने तिला विचारले. बाई श्रीकृष्ण काइ मातीएचा : देवकी काइ मातीएची? स्वमीचे हे विरूद्ध मत ऐकल्यावर तिनें मातीचे गाकुळ करणे सोडलें.[२३] मग खाजी तळिली फुलोरा बांधला जग व्रतस्थ बायकांनी स्वामीची पूजा केली त्याच्या हाती वाण समर्पण केलें बोणेबाईनें उपवास केला होता. तो स्वामीच्या सांगण्यावरून तिने उपवास सोडून भोजन केले.[२४]

७) होळी किंवा सिमगा :–

हिरण्यकश्यपूची बहिण होलीका व भक्त प्रल्हादाची कथा वऱ्हाडात प्रचलीत असून त्यावरून होळीचा सन साजरा केल्या जातो. त्यात शेणाच्या गवऱ्या विविध झाडांच्या पत्त्यांचे हार व उस लावून होळीची पूजा अर्चना करून गावप्रमुख प्रथम होळी पेटवित. व दुसऱ्या दिवशी रंगपंचमीला रंग खेळतात. गोविंदप्रभुचे बालपणीचे सवगळी म्हातारपणी धुळवळ खेळावयास

निघाले. 'चीखलु, माती, राख, कापुरु, कस्तुरी, चंदन, ऐसा खेळू केला'[२५] मांस व दारूचे सेवन करून हा उत्सव साजरा करण्याची पध्दती मेळघाटातील आदिवासी लोकांमध्ये दिसते. त्यांच्यात सतत पाच दिवस पैसा गोळा करून रात्री नाच गाणी यामध्ये रममान होतात. इमादशाही काळात हा सण मोठया प्रमाणात होत असावा असे दिसून येते.

हिंदू धर्मातील व्रत वैकल्य

बहामनी व इमादशाही पूर्वी एलिचपूरचे राज्य म्हणजे यादवाचा मुख्य प्रांत वऱ्हाड होता. यादवांचा मंत्री हेमाद्रीच्या 'चतुर्वर्गचिंतामणी' ग्रंथातील व्रतखंडात वर्णिलेल्या वर्षाकाठी दोनहजार व्रतांवरून यादवकाळात व्रतवैकल्याचे स्तोम बरेच माजले होते असे दिसते.[२६] तसेच यादव काळात अचलपूर येथे यादवांचा मांडलीक राजा रामराजा दरणा हा असून तो अनेक व्रत वैकल्य करीत असत असा उल्लेख आपल्याला महानुभाव साहित्यात अनेक वेळा आढळतो. यावरून वऱ्हाडात मोठया प्रमाणात व्रतवैकल्य केल्या जात होते. मुस्लीम आक्रमणे झाली तरीही हिंदू लोकांनी आपला धर्म जपून व्रतवैकल्य चालू ठेवल्याचे दिसते. नतंर इमादशाही स्थापना होऊन अचलपूर राजधानीचे ठिकाण बनले. तेव्हा पासून तर आजपर्यत बरेच व्रतवैकल्य प्रचलित असल्याचे स्पष्ट होते. मध्ययुगीन वऱ्हाडातील प्रचलित असलेल्या व्रतांपैकी काही व्रतांची माहिती देण्यात येत आहे.[२७]

१) दमणकपर्व :– हे व्रत चैत्र शुद्ध पक्षात हे व्रत येत असे. त्यादिवशी देवाची आणि गुरूची पूजा करून फुले न मिळाल्यास दवणा वाहत असत. दवना एक लवदार सुंगधी औषधी वऱ्हाडात पुजेस वापरत हे आपल्याला महानूभाव साहित्यावरून दिसते. एलिचपूरला चक्रधरस्वामी यांना राजादरणाने दमणपर्वापर्यत महालात ठेवले होते. दमणकपर्वाच्या दिवशी मोठा उत्सव करण्यांत आला राजमातेने आणि राणीवसांतील राजपत्नी, आणि इतर स्त्रियांनी पोडशोपचारें पूजा केली, चरणा वर तुळशी व दवणा वाहिला रामराजा दरणा या राजानेंही स्वत: श्रीचक्रधराची पूजा केली.[२८]

२) श्रावणी:– श्रावण महिण्यात होम हवन करून चार ब्राम्हण नवे वस्त्र धारण करून यज्ञ करीत असत. त्यानंतर उपवास केल्या जाई. जवळपास सूर्याचे मंदिर असल्यास तेथे पुजापाठ करून उपवास करीत. सूर्याचे वऱ्हाडातील उमरावती येथे होते.[२९] तेथे सार्वजनिक रीत्या उपवास केल्या जात असावा.

३) पंचाग्निसाधन :– ज्ञानेश्वरीत ह्या व्रतासंबधाने पुढी माहिती मिळते. तीवरून डोक्यावर गुगुळ जाळणें, पाठीला गळ टोचणें भोवताली विस्तव पेटवून स्वत:चे अंग जाळणें उलटें टांगून घेऊन धूणीवर धुम्रपान करणे, हे प्रकार या व्रतांत येतात.[३०] या खेरीज एकांतर आणि चांद्रायण व्रत इत्यादि व्रतांचे उल्लेख ज्ञानेश्वरीत व लीळाचरित्रादी महानुभाव वाङ्मयात आढळतात. येथे हेमाद्रीच्या व्रतखंडातील नमूद केलेल्या व्रतवैकल्याची यादी दोन हजार व्रताची माहिती दिली आहे.[३१] विराज ही माहिती येथे देणे शक्य होत नाही कारण ती फार मोठी आहे.

निष्कर्ष : मध्ययुगीन काळात वऱ्हाडचे राज्य अचलपूर या राजधानीतून चालत असे. येथील सर्व सुलतान हिन्दूचे मुसलमान झाले होते. त्यामूळे धर्मवेळेपणा कमी झालेला होता. आणि म्हणूनच वऱ्हाडात हिन्दूंना आपली संस्कृती जोपासता आली. वऱ्हाडातील स्थानीक कारभार देशमुख, देशपांडे, कुळकणी, पाटील, यांच्याकडे देण्यात आल्याने ग्रामीणच नव्हे तर शहरी भागात पोळा, दिवाळी, दसरा, विविध व्रतवैकल्ये करण्याचे स्वतंत्र असल्याचे दिसून येते. बहुतांश समाज हा शेतकरी, मजूर, कारागिर, असून अशिक्षित होता तरीही धार्मिक सेस्काराने नैतिक गुणाने श्रेष्ठ होता. त्यामूळे विविध सण मध्ययुगीन काळात प्राचीण सणांची परंपरा जोपासण्याचे कार्य अचलपूर राज्याने प्र्यायाने वऱ्हाड प्रांताने केले तेच आज महाराष्ट्राची सण, व्रतवैकल्य, ही संस्कृती म्हणून गणल्या जाते.

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Synthesis of Graphene Nanocomposite for Biosensor Application used in Cholesterol Detection

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Abstract: *Study of Graphene & its application for the functionalized graphene nanocomposite in the field of biosensing. A non-enzymatic approach towards cholesterol detection has been presented, exploiting the electrochemical non enzymatic route of sensing which has a distinct advantage over other conventional enzymatic processes. Chemically converted Graphene modified with* β-Cyclodextrin *(β-CD), being hydrophilic, electroactive and high surface area material, provides a platform for the electrochemical detection of cholesterol using Methylene Blue as redox indicator. Methylene Blue (MB) forms an inclusion complex with Grp-β-CD and emerges as a cholesterol sensing matrix. MB molecule is replaced by cholesterol molecule and moves out in the buffer solution, hence, detected electrochemically using Differential Pulse Voltammetric (DPV) technique.*

Keywords: *carbon, human body, field of Biosensing, graphine nanocomposites, sensor*

Introduction

Graphene has become the most exciting nano-structured carbon allotrope over the lastfew years, gaining its popularity in various fields of material research including energy storageand conversion [1], electromechanical resonators [2], ultrafast electronic devices [3] etc. Applications of graphene have recently been extended even to biological research viz., in bioelectronics [4], drug delivery [5-7], molecular resolution sensors [8- 10] because of its large specific surface area, extraordinary electrical and thermal conductivities [3,11], high mechanical stiffness [12], good biocompatibility [13], and lower manufacturing cost [14]. As the high electrical and thermal conductivities of graphene originate from the extended long-range π-conjugation, it helps in enhancing its usage in electrochemical approach for biosensors [15] which is one of the most emerging fields in recent biological science. Grapheneals exhibits a broad electrochemical potential and low charge-transfer resistance, making it almost ideal for multifunctional fast sensors. Another important feature required in electrochemical biosensors is the ability to be functionalized. Graphene and graphene oxide (GO), both are versatile materials for chemical functionalizations.

Cholesterol is a fat-like substance that human body requires to function properly, as it isneeded to form cell membranes, some hormones and bile acids. Cholesterol and its esters are membrane constituents widely found in biological systems which serve a unique purpose of modulating membrane fluidity, elasticity, and permeability [16]. It makes the cell walls rigid and strong, protecting itself from the foreign bodies. In the human serum, 80% of cholesterol existsin the ester form. Extra consumption of cholesterol through foods can build up on the inside walls of the arteries and over the time, cholesterol build up, called plaque, can narrow the spacefor blood to flow through. The normal level of total cholesterol in healthy human serum is ~180 to 200mg/dL [17] where higher levels of cholesterol lead to life-threatening coronary heart diseases, cerebral thrombosis and atherosclerosis [18]. Therefore, cholesterol level in the serum is one of the most important parameters in diagnostics and prevention of heart diseases. Over various analytical methodologies, the electrochemical approach for bio-sensing has gained momentum in past few decades, due to their high sensitivity and fast response time. The electrochemical bio-sensing of cholesterol has been performed by the enzymatic reaction of cholesterol with cholesterol oxidize, where the concentration of either H_2O_2 generated or oxygen consumed during the enzymatic reaction is being monitored [19]. Detection selectivity in most of these methods relies on the use of cholesterol selective enzymes which are expensive and prone to denaturation as an alternative for simple and cost effective.

Macrocyclic hosts such as crown ethers, cryptands, cyclophanes *etc.* have received much attention so far, opening a wide range of opportunities for new supramolecular materials. Among them, cyclodextrins (CDs) are the most important and promising macrocyclic hosts because they are water-soluble natural products, inexpensive, commercially available, nontoxic and readily functionalized [20-23]. It is well known that β-Cyclodextrin (β-CD) is a cyclic oligosaccharide consisting of 7-β (1-4)-glucopyranose units. The internal cavity is lined with C(3)H and C(5)H hydrogen and ether-like oxygen that provide a hydrophobic environment, whereas the external faces of the cyclodextrin molecule are hydrophilic. Due to its ability to encapsulate hydrophobic compounds (Figure 1), this internal cavity of β-CD allows hydrophobic cholesterol molecules to be soluble in aqueous solutions [24,25].

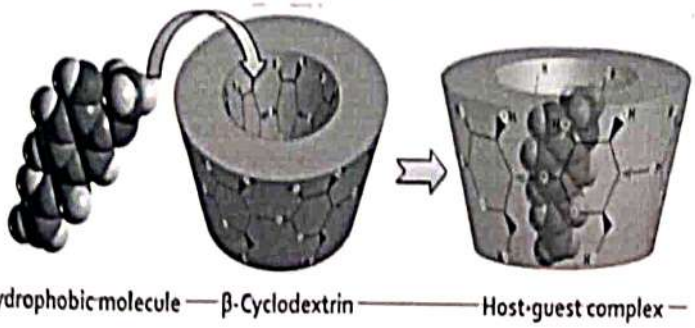


Figure 1 A schematic representation of Host-guest inclusion complex formationin β-Cyclodextrin

β-Cyclodextrin (β-CD)s have a high affinity for sterols as compared to other lipids *in vitro* [26,27], which make these compounds quite effective in modifying cholesterol metabolism. Mondal *et al.* have recently carried out fluorescent detection of cholesterol using same Graphene-β-CD hybrid system, where the optical detection of cholesterol was carried out using Rhodamin 6G (R6G) dye as a fluorophore [28]. But, to achieve higher detection sensitivity along with lower detection limit and reproducibility, electrochemical sensor delivers more authentic results than optical. In order to harness and utilize the properties offered by graphene and β-CD molecule, we adapted a non-enzymatic electrochemical approach for cholesterol sensing using Graphene-β-

Cyclodextrin (Grp-β-CD)hybrid system as the sensing matrix.

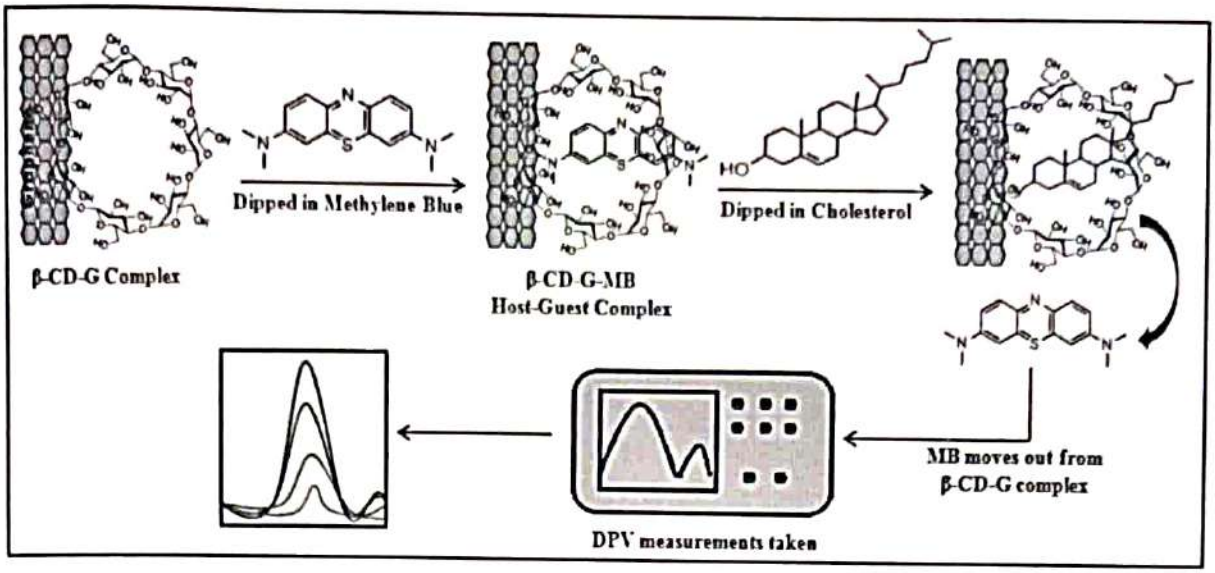


Figure 2 Scheme for Mechanism of cholesterol sensing, using Graphene-β-Cyclodextrin (Grp-β-CD) as theworking matrix

Graphene-β-Cyclodextrin (Grp-β-CD) solution was synthesized *in situ* following the route proposed by Guo *et al.*[29] where treatment of GO (Graphene oxide) with β-CD in presence of ammonia and NaOH was carried out. β-CD is presumed to get covalently attached over GO sheets during the reaction forming GO-β-CD. This complex was then reduced using hydrazine, forming Grp-β-CD. Methylene blue (MB), a redox indicator, when added into the Grp-β-CD solution, forms a host- guest complex with β-CD, as demonstrated schematically in Figure 1 [30,31]. On addition of cholesterol in the solution, the cholesterol molecule will replace the MB molecule in the cavitydue to its higher affinity towards β-CD, offering better detection sensitivity range via selective host–guest interaction and graphene sheet network helps in rapid transfer of the electrochemical signal (in Figure 2). As MB is a well known redox probe and hence can be easily detected using Differential Pulse Voltammetry (DPV) technique. Although there are sample reports in the literatures on the non enzymatic electrochemical or optical biosensing proceduresfor detection of different analytes, to the best of our knowledge this is for the first time, a completely non-enzymatic sensing with high sensitivity and low detection limit is being reported, using an electrochemical DPV metric method with the targeted analyte cholesterol.

Synthesis and electrode preparation

Synthesis of β-Cyclodextrin Functionalized Graphene from Graphene Oxide

Grp-β-CD was synthesized Hummer's method reported earlier [25] with some minormodification. Aqueous solution of GO (5.5 mg/mL) was prepared by modified Hummer's method [32]. In a separate vial, 420 mg of β-cyclodextrin was dissolved in 20 mL water and mixed with 200 µL NH_4OH and 1 mL GO solution. The whole solution was continuously stirred for an 1.5 hour, followed by addition of 20 µL hydrazine monohydrate solutions (0.05 M). Next, the solution was heated to 80-90° C for an hour with constant stirring. The stable black solution was then dialysed against distilled water with cellulose membrane for overnight. Finally, the solution was diluted with 0.1 M Phosphate Buffered Saline (PBS) of pH 7.4 and used as stock solution for the cholesterol sensing.

For the characterization of the sensing material, Transmission Electron Microscopy (TEM), FT-IR and Raman Spectroscopy were carried out. The TEM images weretaken using a transmission electron microscope (FEI model Tecnei G2 20S with 200 kV accelerating voltage and resolution range of 50 nm to 1µm). FT-IR (Perkin Elmer model Spectrum 100) was done to identify the nature of bonding occurring between β-CD and

Graphene sheets, whereas Raman spectroscopy was performed (Horiba Raman triple spectrometer T64000 with Ar ion Laser and sample imaging using Olympus 50X microscope) tocharacterize the nature of the graphene sheets.

Preparation of cholesterol solution

As cholesterol has very low solubility in water, 1 mM stock solution of cholesterol was prepared by dissolving 4 mg of cholesterol in 10 ml ethanol. The prepared solution was used further for the electrochemical detection. The cholesterol solution gets solvated in PBS buffer, during its sequential additions in the electrochemical cell.

Preparation and functioning of the sensing probe

For the electrochemical studies, a Potentiostat / Galvanostat from Princeton Applied Research (Model 263A) having PS Lite software were used, connected with a single compartment cell with three electrodes (here counter as well as working electrode is Pt wireand an Ag/AgCl electrode acts as a reference electrode respectively). Initially, 3.5 ml Grp-β-CD solution (solvated in PBS, maintained at pH of 7.5) was taken in the electrochemical cell. 2 ml, 10 mM Methylene Blue (MB) solution was then added and kept for a while. As suggested earlier, MB molecules are expected to move inside the cavity of the β-CD molecules, forming an inclusive complex of Grp-β-CD-MB (the sensing probe). The sensing probe was then centrifuged, separated and washed thoroughly to remove the MB traces remaining on the surface. The residual probe was transferred again to the electrochemical cell with 3.5 ml fresh PBS solution, assuming it as a blank solution. The CV and DPV measurements were carried out before and just after mixing with sequential addition of stock cholesterol aliquots. CV plot wastaken at a scan rate of 10 mV/s, within the potential window of -0.7 to 0.7 V. DPV scan was taken with pulse height of 50 mV and pulse width of 70 ms. Stock solution of cholesterol wereadded to it, in such a manner that its final concentration in the system would increased from 0 to100 μM. Due to its higher binding affinity towards β-CD, cholesterol molecules are expected to replace the MB molecules, forming Grp-β-CD-cholesterol complex and the extent of MB molecule moving out of the graphene-CD system, would be detected by DPV and CV measurements after each addition. Initially the sensing probe was characterized using Cyclic Voltammetric (CV) measurements, to ensure the potential window required for the DPV.

Results and Discussions

During the synthesis of Graphene-β-Cyclodextrin (Grp-β-CD), initially when graphite is treated in the presence of strong oxidizing agent, $KMnO_4$ and mixed acid (H_2SO_4/H_3PO_4), polar oxygen functionalities developed on the graphitic sheets lead to the formation of GO. And, these oxygen functionalities (mostly epoxy, hydroxyl, carbonyl and carboxyl groups) render hydrophilic nature, thus making GO soluble in water [15,33]. During reduction with hydrazine, chemically converted Graphene (CCG) sheets agglomerate due to strong π-π stacking interactions with less number ofhydrophilic functional groups on the GO sheets [32]. During reduction of GO in the presence of β-CD, covalent interactions occur between hydroxyl groups of β-CD and oxygen functionalities of GO, hence

forming water soluble Graphene-β-CD system (Figure 3(a)) [29,34,35].

Transmission Electron Microscopy

The images obtained from TEM for Grp-β-CD sheets, showed few discrete agglomerations on the graphene sheet, possibly for β-CD which is covalently attached on its surface (Figure 3(b)). From the TEM image, the presence of agglomerated β-CD was established over the sheet like structure of graphene, but in order to justify the covalent attachment, FT-IR studies were conducted.

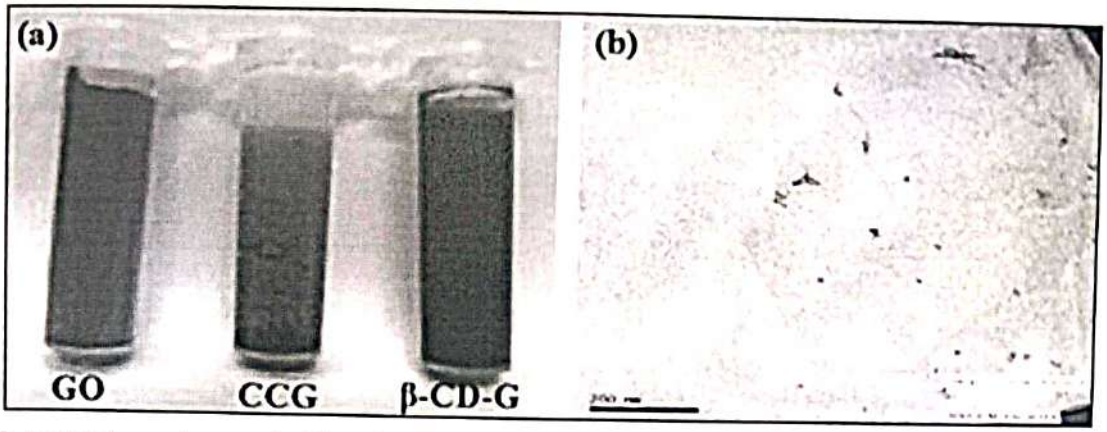


Figure 3 (a) Colour change in Graphene Oxide (GO), Chemically converted graphene(CCG) and Graphene-β-Cyclodextrin hybrid (b) TEM image of the graphene sheet withthe spotted area showing the agglomeration of the attached β-CD

FT-IR studies

The characteristic FT-IR spectral signal of β-CD can be observed in the spectra of Grp- β-CD (shown in Figure 4), justifying the covalent interactions occurring between β-CD and CCG and no physical adsorption of β-CD over graphene sheets. The characteristic peaks of 3380 cm^{-1} due to stretching vibration of O-H, 2935 cm^{-1} due to C-H stretching vibration, C=Ostretching vibrations gives a pick at 1730 cm^{-1} bending stretching of C-H from CH_2 and CH_3 gives a peak at 1430 cm^{-1}, 1157 cm^{-1} is due to coupled stretching vibrations of C-O, C-C and C-O-H, and 937 cm^{-1} peak represents skeletal vibration involving α-1,4 linkage in Grp-β-CD. ForCCG, the characteristic peaks are mainly at ~3380 cm^{-1} due to stretching vibration of O-H (a small peak due to the presence of O-H groups in the graphene sheets after de-oxygenation of GO), and 1070 cm^{-1} is due to stretching vibrations from C-O, from the carboxyl groups remaining after hydrazine reduction. The spectrum of our sensing matrix, Grp-β-CD showed the mixed characteristic peaks of β-CD and CCG, indicating the successful covalent attachment of these two [29].

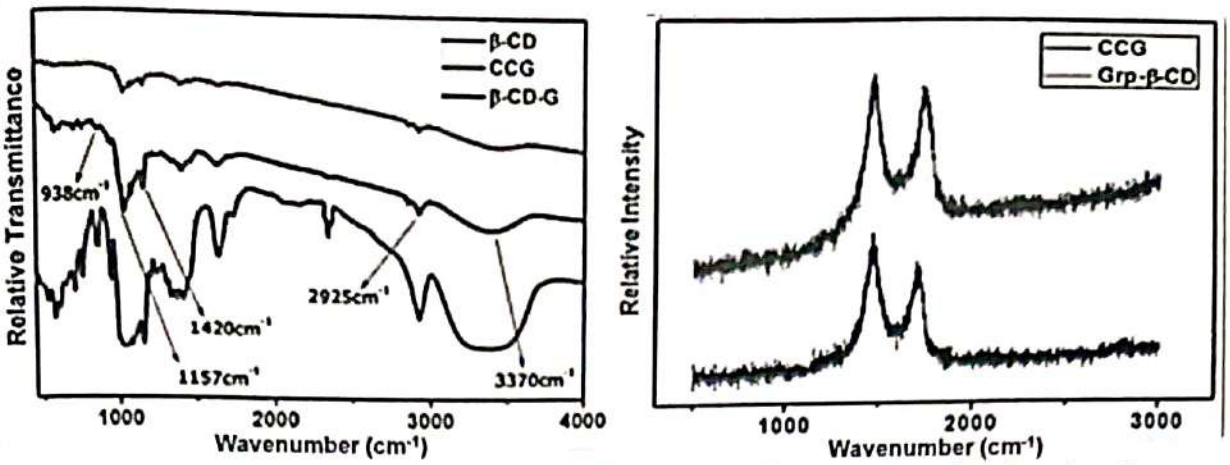


Figure 4 FT-IR spectra for CCG, β-CD and Grp-β-CD composite showing the signature of β-CD along with graphitic peaks; Raman spectra for CCG and Grp-β-CD

Raman Spectroscopy

The Raman Spectra (Figure 4), for the CCG and Grp-β-CD system showed D and Gpeaks at ~1470 and 00 cm^{-1} respectively, significant for the pristine graphitic nature in the CCG as well as in Grp-β-CD, even after β-CD was incorporated within the graphene sheets. The two spectra do not show any major changes in the peak positions or intensities establishing thefact that graphene didn't lose its graphitic structure after binding with β-CD.

Electrochemical studies for the sensing matrix

Cyclic Voltammetric (CV) studies were employed as an electrochemical characterisation tool for the sensing probe of cholesterol sensing. CV plots were taken at a scan rate of 10 mV/s, in the potential window of -0.7 to +0.7 V, for the Grp-β-CD solution in PBS, before and after dipping into MB (Figure 5 (a)). Cyclic Voltammograms showed that MB quite efficiently displayed changes in the peak current value between -0.1 to +0.1 V (as shown in Figure 5 (b)). Further addition of cholesterol in the system also exhibited significant changes in the peak current. Hence, CV results confirmed that MB is giving a peakcurrent around -0.1 V potential [30]. Therefore, we chose the working window for DPV studiesin the range of -0.5 to +0.5 V. Comprehensively, the trends in the peak position and intensity obtained in cyclic voltammograms, helped us in the better understanding of electro-activity of our Sensing probe along with the selection of the potential window for further DPV measurements. Progress of MB replacement by cholesterol is manifested in a monotonic increase of the electrochemical signal of MB in DPV with increase of target cholesterol concentration.

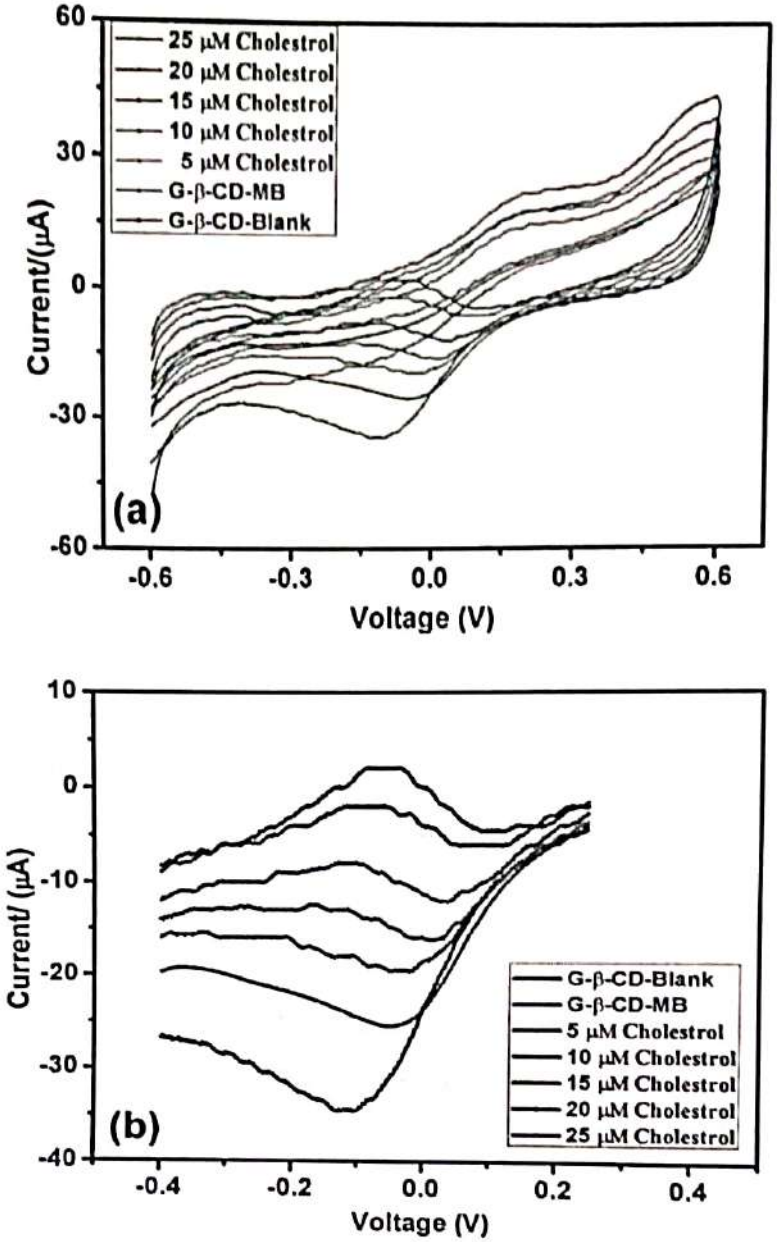


Figure 5 (a) Cyclic Voltammograms of the Grp-β-CD sensing probe in the PBS (at pH7.4) for the additions of analyte, cholesterol; (b) The peak variations occurring, after cholesterol additions in the range of -0.3 to 0.3 V

It can be seen that initially, when the cholesterol concentration was zero, there was no MB peak in the 0 to +0.4 V regions even when the MB is present in the Grp-β-CD (Figure 6). This indicates thatthe MB is bound in the cavity of the β-CD therefore, not able to give any redox signal into the electrode.

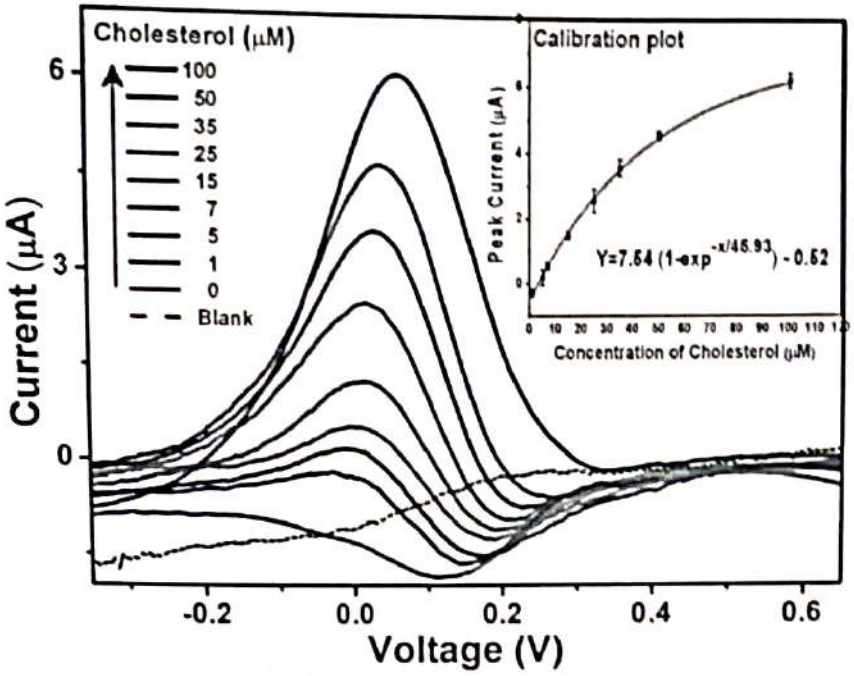
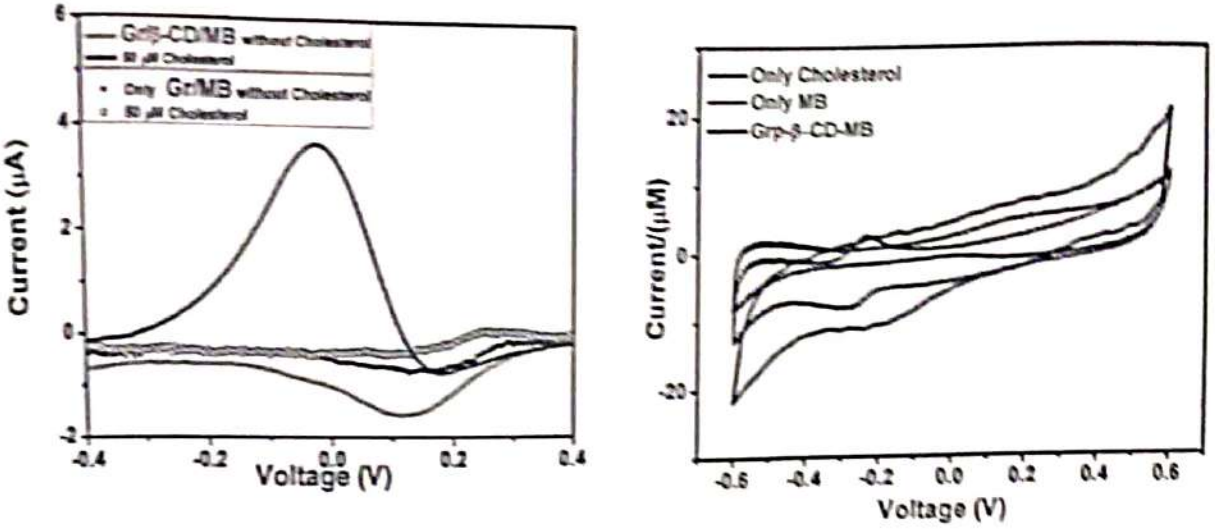


Figure 6 DPV of the Grp-β-CD sensing probe in the PBS after addition of analyte, cholesterol, starting concentration from 1 to 100 μM. Calibration plot of analyte concentration dependent peak current value is given with its fitted curve in the inset.

Though there is some probability of MB, which is hydrophilic in nature, to get adsorbedin the graphene sheets, these will not make any difference to the CV and DPV results, as MB remains intact on the surface of graphene sheets in the beginning as well as at the end of the experiment. A control experiment carried out to exclude the possibility of desorption of MB from the graphene surface during cholesterol detection proved that only the MB molecule coming out from the CD cavity is responsible for the DPV signal (Figure 7). Control experiments using CV were also performed to establish the significance of the Grp-β-CD matrix, as compared to bare MB or cholesterol. After addition of the cholesterol, it readily moved insidethe cavity of the β-CD, replacing the MB into the solution and hence, a characteristic peak was obtained at +0.05 V. Cholesterol can only go inside a hydrophobic pocket (that is of β-CD) and would replace MB molecule, as cholesterol has higher affinity towards CD as compared to MB.The measured binding constant between cholesterol and β-CD-G was ~1.7 M^{-1} which is similar to the earlier observed value with free β-CD [36]. The sensing signal of Grp-β-CD system increased periodically with increasing concentration of cholesterol, up to 100 μM, as presented in the calibration curve (Figure 6 inset). Above 100 μM, the signal reached its saturation. Detection limit was less than 1 μM which was quite low and satisfactory with respect to other recently reported articles.

Figure 7 Comparative studies for Grp-MB and Grp-β-CD-MB, before and after theaddition of 50 μM cholesterol, to establish the significance of Grp-β-CD matrix



Immobilization matrix	Method of immobilization	Detection range (mM)	Detection Process	Sensitivity	Sensing Time (s)	Reference
Tetraethylorthosili-cate ChOx/HRP	Covalent	2–12	Amperometric	-	-	37
Tetraethylorthosili-cate ChEt/ChOx	Covalent	0.184–12	Photometric	8.3×10^{-7} Abs/mM	180	38
Dithiobissuccinim-idyl ChEt/ChOx	Covalent	0.77–6.14	DPV	-	-	39
GC/CS–SiO_2–MECNTs ChOx	Entrapment	0.004 - 0.7	CV	1.55 μA/mM	13	40
CHIT-SiO_2-MWCNT/ITO ChET/CHOx	Covalent	0.15–7.68	DPV	3.8μA/mM	10	41
ChOx/nano-ZnO/ITO	Sol-Gel entrapment	0.278–22.2	CV	0.059 A/mg $dl^{-1}cm^{-2}$	10	42
Grp/β-CD/ Rhodamine 6G	Entrapment	0.005-0.03	Fluorescence	Micromolar range	-	28
Grp/β-CD/ Methylene Blue	**Entrapment**	**0.001-0.10**	**DPV**	**0.01 μA/μM**	**~20**	**Present work**

Table 4.1 Comparison of the present work with other recent literatures, using various immobilization matrix and techniques for cholesterol sensing

Table 4.1 illustrates few of the recent literatures on cholesterol biosensors, through both enzymatic and non-enzymatic sensing routes, establishing the edge ofthe present work. The detection limit and sensitivity of the present sensing matrix is comparatively better than the reported ones, with a decent sensing time. The peak potential ofMB showed a little shift towards the positive potential. Being a pH dependent redox indicator, the peak potential of MB shifted from 0.05 to 0.1 V with decreasing pH, as the cholesterol solution used in DPV was soluble in acidic buffer. Therefore, in the higher concentration range, the MB peak in DPV shifted slightly towards right. The cyclic stability of the sensing matrix was also tested, before and after the addition of 10 μM cholesterol solution, by performing 100 cycles in cyclic voltammeter at a scan rate of 100 mV/s, in the potential window of -0.7 to +0.7V. It is evident from obtained voltammograms that the sensing matrix was quite stable towards its cyclability (Figure 8).

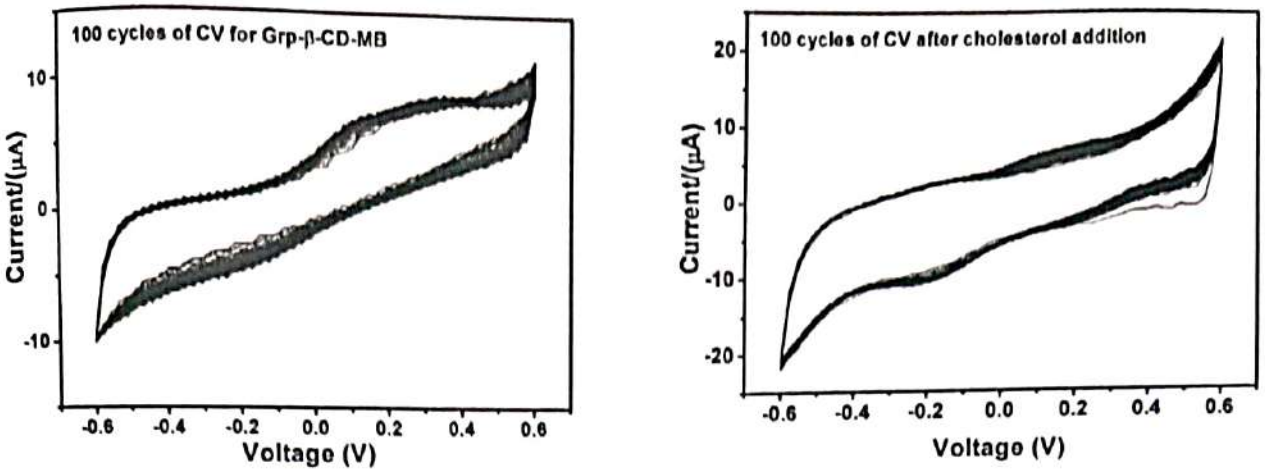


Figure 8 Cyclic voltammograms illustrating the cyclability of the sensing matrix (Grp-β-CD-MB) before and after addition of 10 μM cholesterol solution.

Interaction of the Interfering Species

As we know, human blood serum contains many more bio components like salts, amino acids, carbohydrates, lipids etc., those can interfere with cholesterol detection and hamper the selectivity of the biosensor. Therefore, we studied a wide range of response in DPV for the species which can interfere with the detection process of cholesterol in the blood serum. It is quite evident from Figure 9 that salts like NaCl, KCl and $MgCl_2$; carbohydrates and amino acids like glucose, glycine etc. showed negligible interference even at the concentration of 2 mM, except tryptophan. Anionic surfactant like Sodium Dodecyl Sulphate (SDS) showed minute interference in the system, compared to cholesterol detected for only 30 μM concentration.Similarly, few hydrophobic drugs (lidocaine, chloropramine, quinine, quinidine and piroxicam) were checked for their interference with cholesterol. Results obtained showed very little interference for 2 mM drug concentrations against 30 μM cholesterol concentration.

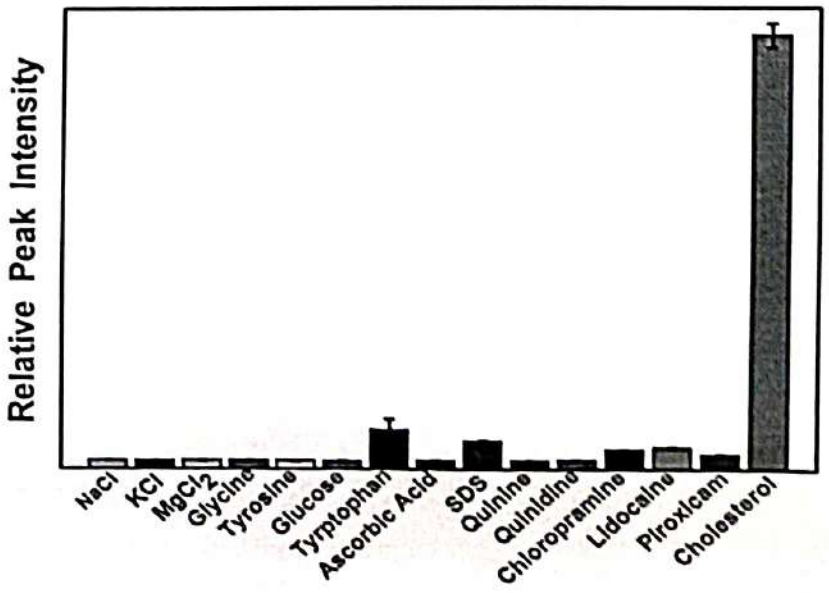


Figure 9 Comparative interference studies of different species in the developed cholesterol detection method, using DPV and keeping all the parameters constant. Thecholesterol concentration is 30 μM against concentration of other substances at 2 mM.

Conclusion

In this work, we have developed an electrochemical method of cholesterol detection using β-CD functionalized graphene. The detection limit of cholesterol is achieved as low as 1μM which is quite impressive compared to recent literatures. Salient features of the present study include:

1) Graphene increased solubility after β-CD functionalization, due to the covalent interactions occurring between the hydrophilic surfaces.

2) The sensor can easily detect cholesterol using DPV technique, where cholesterol molecule isreplacing MB molecule and forming the inclusion complex within the hydrophobic core of Grp- β-CD.

Also, the developed detection method is important as it does not use any enzyme or antibody for detection and still, detects cholesterol efficiently in the micro molar concentrationrange with outstanding selectivity over the common interfering species. To the best of our knowledge this is for the first time, a completely non-enzymatic sensing with high sensitivity and low detection limit is being reported, using an Differential Pulse Voltametric (DPV) technique with the targeted analyze cholesterol. The developed biosensing technique for cholesterol is a quick, cost effective and reliable, which is an important parameter for its real-life implementation in medical science.

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Review on the advantages of polymer based batteries

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Abstract: *: This reviewed article reports, the discussion on new generation battery material. This polymer based battery materials is different from conventional Li-ion battery. It shows more efficiency, durability, flexibility, high power densities, high efficiency and a lot advantage over the Li-ion batteries. Polymer based battery materials should be the better alternative anodes for high performance lithium-ion batteries.*

Key Words: *Polymer; Lithium; Electrode; Battery.*

1. INTRODUCTION:

Recently, battery is most essential part in daily life. The daily life is completely depends on batteries from smallest battery like coin cells to batteries for watch, torch, mobile phones, laptops, as well as batteries for vehicles. Moreover, batteries for electric vehicles like bike, cars, buses, trucks as well as energy storage batteries. This demand is not accomplish by a single type of battery, it need different types of batteries. Because of this reason, each and every demand have need of different size and capacity of battery. So, each battery needs different chemical composition. In last decade polymer based batteries get more attention as compared to Li-ion batteries. The polymeric materials replace the use of metal in electrodes which results in enhancement in battery applications. The redox-active polymeric material is used as active materials for battery. These materials enhanced the life and efficiency of battery. The Li-ion batteries have some limitations like natural resources, mechanical robustness, electrochemical performance, environmental issues, and cost. So, in recent years these batteries are outdated and polymer based batteries taking advantage over it. Because of their advantage such as capacities, fast redox kinetics, structural design ability, low cost, potential cheapness, and environmental friendliness also possess good processability and mechanical flexibility. Old generation batteries use metals as redox-active materials but these batteries are based on organic materials as the active parts within the electrodes. Due this up gradation properties like flexible batteries fabrication, high power densities, high efficiency and many more are held by these fabricated batteries [1-15]. So that recent researchers have more research interest in polymer based batteries which have high commercial interest. Therefore, in this article the polymer based battery materials are reviewed.

2. RESULTS AND DISCUSSIONS:

This section based on the discussion on experimental technique and results reported by various researchers. Zhang et al. synthesized triphenylamine-based microporous organic polymers with high surface area were employed as cathode materials for lithium ion batteries. The materials were characterized to confirm the formation of expected material through Fourier-transform infrared spectroscopy (FT-IR) spectrum of OPTPA, thermal properties like TG/DTA to confirm the thermal stability, the porosity of OPTPA, SPTPA and YPTPA was determined by nitrogen adsorption and desorption at 77.3 K, volumetric adsorption analyze .The microscopic features of the sample was done on a field emission microscopy (HRTEM) and scanning electron microscopy (SEM) high-resolution transmission electron microscopy to study the surface properties. It reveals excellent results like the high discharge capacity, excellent rate performance, high stable cyclability and high energy density. Author expected these porous organic polymers based battery materials could be capable for the fast charge discharge cathode materials of lithium ion batteries [16]. Kanga et al. reported the synthesis of photocured PEO-based solid polymer electrolyte as well as its application to lithium-polymer batteries. Moreover, the materials reveal the tremendous results. The reported materials show the maximum conductivity value was 5.1 S/cm at room temperature. Also, the reported electrolyte materials represent the oxidation stability up 4.5 V as compared to lithium reference electrode [17]. Sha et al. synthesized graphene/chemically-

crosslinked PMMA (Gr/c-PMMA) composites in the presence of GO as alternative anodes for high performance lithium-ion batteries. The prepared material was characterized via Scanning electron microscopy (SEM) for surface study, Fourier transform infrared (FT-IR) spectra, X-ray diffraction (XRD) analysis for structural confirmation, Thermogravimetric analysis (TGA) was measured on at 10°C min-1 under an Argon atmosphere for thermal stability investigation. Also, X-ray photoelectron spectroscopy (XPS) analysis was carried out. It reports the Gr/c-PMMA anode provides a large capacity of 206 mAh g-1 at 20 mA g-1, and retains 167 mAh g-1 at a high rate of 400 mA g-1 [18]. X. Yue et al. explored the synthesis via cationic radical polymerization, characterizations and application of two composite materials such as supercapacitor carbon (SC) loaded with poly [2,3-bis (2-pyridinyl)-5,8-bis (2-thiophenyl) quinoxaline] (PPTQ) or poly [2,3-bis (2-pyridinyl)-5,8-bis (2-(3,4-ethylenedioxythiophene) quinoxaline] (PPETQ). The reported material had good electrical conductivity and delivers much more active sites for the lithiation/delithiation redox process due to its honeycomb porous structure [19]. Number of researchers had reports there research articles for the study of polymer based battery materials. But, in this review article some articles are discussed on the basis of their performance ability, characterization methods, and material selection. These articles contain good material selection as well as reveals better results to replace conventional battery electrodes.

3. SUMMARY:

The conventional battery electrodes/materials could be replaced by the polymer based composites. Reviewed articles shows the good results of prepared materials which could replace the old generation battery materials with more efficiency, higher charge density. The reported polymer based materials better efficiency as compared to conventional battery materials.

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A review: New era of polymer based corrosion coatings

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Abstract
The review article reports the new materials like polymer based corrosion protection coatings. The various synthesis methods adopted by the researchers and characterization carried out for the confirmation of materials such as XRD, FTIR, UV-Vis, SEM, EDS, EIS, Cyclic Voltammetry (CV), potentiostatic and galvanostatic conditions are discussed. The various polymers and their copolymer as well as grapheme doped polymer are got tremendous anti-corrosion protection results which showing maximum 98% of efficiency.

Keywords: XRD, FTIR, UV-Vis, SEM, EDS, EIS, Cyclic Voltammetry (CV)

Introduction
Nowadays metals are basic content for the electronics devices, instruments, pipelines, construction, marine, aeronautics, automobiles industries, and machinery parts, etc. These metals things could be deteriorated due to corrosion and therefore they may require replacement which is very costly. Metal rods are the main structure in construction which placed inside the concrete, due to concrete it should be degrades that results in weak construction and decrease the service life of construction structure. Therefore, researchers got tremendous innovative research interest towards synthesizing the materials which can protect these important things from corrosion. The research for the development of anticorrosion materials is new era of research in both scientific and industry communities. Researchers are continuously trying to prepare the new and enhanced anticorrosion materials for better service life. Recently, polymers are main focus of research in anticorrosion materials due to they demonstrate good barrier properties, ease of altering properties and massive production. Also, polymer based anticorrosion materials have the properties like environment friendly nature, good environmental stability, good conductivity and low-cost production. Therefore, most of research is going on preparing the polymer based anticorrosion materials [1-11]. This review article is reports the research carried out regarding the synthesis and characterization of anti–corrosion materials based on polymer and their copolymer composites.

Results and discussions
The most researchers found the best results by synthesizing the polymer based anti-corrosion coating materials. Dagadag *et al.* synthesized and studied the polymer based epoxy resin TGEDA-MDA as effective anti-corrosive coating for steel. They found best results such as PDP reveals the anti-corrosion efficiency for the TGEDA-MDA near about of 93%. Moreover, EIS investigation reflects best results as effective anti-corrosive coating at metal-electrolyte interfaces for DGEDDS-MDA [7]. Rangel-Olivares *et al.* fabricated the nanocomposites of metal oxides (SiO_2, CeO_2, and TiO_2A) doped polyaniline through in situ chemical oxidative polymerization by rapid mixing and characterized via XRD, FTIR, UV-Vis, SEM, EDS, EIS. Results showed that TiO_2APANI/AR system, reveals excellent anti-corrosion protection of the steel as compared to other metal oxide based PANI nanocomposites. The TiO_2A/AR nanocomposites reveals the highest protection efficiencies with values 98.63 and 97.93%, SiO_2/AR nanocomposites reflects 97.35 and 97.52% and CeO_2-PANI/AR nanocomosites showed 94.28 and 90.96%. These results showed best efficiency for anti-corrosion of steel [12]. Zhang *et al.* prepared the novel carbon nanotubes of Layered double hydroxides (LDH-MoO_4) by using a facile in-situ growth method. The synthesized nanotubes are characterized via XRD, FTIR, UV-Vis, SEM, TEM, EDS, EIS.

They found best efficiency for anti-corrosion protection [13]. Mathew *et al.* Fabricated the styrene butadiene rubber/polyaniline (SBR/PANI) composites through the electro-polymerization method by using potentiostatic method. The obtained styrene butadiene rubber/polyaniline (SBR/PANI) composites materials represents the best anti-corrosion protection results in different media like acid and neutral media through the studies like Tafel polarization curves, OCP scan and EIS investigation [14]. Elhalawany *et al.* synthesized some conducting polymers nanoparticles (CPNs) such as poly anisidine (PAns), poly toluidine (PTol) and their copolymer (CCPNs) through mini-ia emulsion polymerization for anti-corrosion protection of metals and characterized via GPC, FTIR, TEM and DSC. They found that the presence of conducting polymers nanoparticles and conducting copolymers nanoparticles in the paint can be extremely improve the resistance quality of the formed paint films against corrosion, wash-ability and weathering effect [15]. Jadhav *et al.* synthesized Polypyrrole/Fe_2O_3 and PPy/Fe_3O_4 composites through iron electrochemically and it provide decent corrosion protection to mild steel [16]. Baldissera *et al.* prepared novel epoxy resin (EP)-based coating system containing polyaniline (PAni) as an anticorrosive agent for the corrosion protection of mild steel. The synthesized materials an EP/PAni-EB (emeraldine base), EP/PAni-ES (emeraldine salt), EP/SPAN (PAni sulfonated), EP/PAni-fibers, EP/PhoZn (zinc phosphate), EP/ChroZn (zinc chromate) or EP/Charge were coated on mild steel samples and investigated in 3.5% NaCl solution and found the best anti-corrosion effect [17]. Sathiyanarayanan *et al.* represents the corrosion protection performance of Polyaniline coating on stainless steel and investigated using Cyclic Voltammetry (CV), potentiostatic and galvanostatic conditions [18]. In this section we discussed on the research done by various researchers on the polymer based anti–corrosion materials which showed the best results for anticorrosion tests.

Conclusion

The polymers, conducting polymers, copolymers and their composites as well as nanocomposites represents the excellent results for corrosion protection directly as well as can be blend in the paint. Most of researchers got tremendous results for anti–corrosion. The results reveal 95-98% efficiency for anti–corrosion protection. The results show that these anti-corrosion materials have great application potential in commercial industry.

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DETERMINATION OF ANTIBACTERIAL POTENTIAL OF MELGHAT HONEY SAMPLES

Kshitij N. Shah[1]

ABSTRACT

Honey is a natural product used for the treatment of many diseases due to its anti-microbial, anti-oxidantal, and anti-inflammatory potential. Melghat, a tribal region of Maharashtra, is full of a variety of forests and honey is a prime jungle product, basically collected by the tribal people from the hives of wild bees. In the present study, the antibacterial potential of the Melghat honey samples from four different locations was evaluated by using the disc diffusion technique. The samples were collected and examined in 2019. The antibacterial potential of the Melghat honey samples was detected against six species of bacteria, three from each gram-positive (*Staphylococcus aureus, Bacillus subtilis, and Bacillus cereus)* and gram-negative (*Escherichia coli*, *Salmonella typhi,* and *Pseudomonas fluorescens)*. Except for bacteria *E. coli,* all of the honey samples tested positive against all of the bacterial species tested. Surprisingly, no honey sample showed its activity against the bacteria *E. coli*. The results showed that the Melghat honey has good potential against bacteria and therefore must have tremendous therapeutic properties. It is concluded that there is a greater need for research to explore the antimicrobial properties of Melghat honey.

(Key words: Melghat, Honey, Antibacterial, Chikhaldara, Amravati)

INTRODUCTION

Due to the development of resistance of microorganisms to recent drugs, there is a need to use natural materials against microbes. Honey is one of these materials, that has the potential to work against the pathogens in various diseases. The ancient Indian medicinal therapy "Ayurveda" has been using honey as a prime ingredient in medicines against many diseases (Boussaid *et al*., 2018). It was reported very firstly in 1982 that the honey shows antimicrobial properties. To date, there are numerous research papers published showing the antimicrobial capacity of honey. Manuka honey showed its activity against more than 60 species of bacteria. Malaysian honey and Egyptian honey, as well as other varieties of honey throughout the world, including India, have shown their potential against a variety of microbial as well as viral species. Many mechanisms have been proposed to justify the reason for the antibacterial activities demonstrated by honey, though it is not entirely unspoken to this day. Some of the factors which are supposed to be accountable for the antimicrobial potential of honey are; generation of hydrogen peroxide; high concentration of sugars; presence of phenolic compounds; presence of compounds that are proteinaceous over and above some physical characteristics such as low pH of honey, its low water activity due to less moisture content, the osmolarity of honey, the presence of the enzymes, as well as the presence of some other unidentified compounds (Khan *et al*., 2018; Kalidasan *et al*., 2017; Ismail, 2017; Mandal and Mandal, 2011).

As reported by Bhoyar *et al*. (2018), Melghat is a region in Amravati district and spread over Dharni and Chikhaldara tehsils. It is a forest area predominantly inhabited by tribal people. Melghat honey is extensively used by the tribal people as food and medicine and is produced from the different nectaries of an assortment of flowers. It is assumed that the honey from Melghat must possess antimicrobial potential. The potential of honey against some selected bacterial species was determined here in this study by applying the standard methods.

MATERIALS AND METHODS

Honey samples were collected from four different locations in Melghat forest and designated as H_1, H_2, H_3, and H_4. The antibacterial potential of these samples was detected against six species of bacteria, three from each gram-positive (*Staphylococcus aureus, Bacillus subtilis, and Bacillus cereus)* and gram-negative (*Escherichia coli*, *Salmonella typhi,* and *Pseudomonas fluorescens)*. The samples were examined for the detection of antibacterial potential by the disc diffusion method (Anonymous, 2011; Tendencia, 2004). The CLAIRO COMBI, i.e. the combined microbial sensitivity discs, were made by using the sterile and special grade filter paper, were used. The paper possessed fourteen projected arms. The tip of each projection arm was carefully soaked into the stipulated amount of chemotherapeutic sample. The discs are found to be very useful for the evaluation of the *in vitro* potential of the materials, which may show their activities as agents

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for some fast-growing bacteria. The antibacterial activities of several difficult species can also be determined by using these discs by diffusing them in agar media.

The method is based on the simple truth that, for any antibiotic substance, the range of the inhibition zone created by the substance is inversely related to the Minimum Inhibitory Concentration (MIC) of the strain, which is estimated by the dilution method provided that the test conditions must be the same. The following procedure was followed for the determination of the antibacterial potential of honey against some bacterial species.

A Mueller-Hinton agar solution, maintained at pH 7.3, was used for the experiment. Petri plates with a depth of approximately 4 millimeters were prepared.

Pure cultures were used for the detection of antibacterial activity in honey samples. Before the preparation of inoculums, the gram staining was carried out. The sterilized wire loop was used for the transfer of colonies. The broth culture was kept in an incubator for five hours at a temperature of 35-37°C. The turbidity was adjusted to the McFarland standard level of 0.5 by adding a solution of $BaCl_2 2H_2O$ and H_2SO_4 as well as sterile broth. The plates were inoculated immediately with the prepared dilute solution. Excess inoculums were removed using a sterile cotton swab.

The combi discs were placed over the surface of the medium in the Petri dish with the help of flame sterile forceps. The disc was pressed by applying a little pressure in order to have complete contact with the medium. The zones of inhibition appeared, showing the extent of inhibition. The diameters of the zones developed at the end of the incubation period were measured.

RESULTS AND DISCUSSION

Discs of size 10 mm were used and the results obtained after 24 hours of incubation at 37°C are given in the following Tables 1 and 2. The zones are obtained as shown in figures 1 to 3.

The zones of inhibition were at their maximum value for the bacterial species *S. typhy* in three honey samples *viz.* H_2, H_3, and H_4 while it is on the second position for sample H_1. It was found from the results that all the honey samples showed their activities against almost all the bacterial species. The Melghat honeys showed their highest activity against the gram negative bacteria *S. typhy*. On the contrary there was no evidence obtained to show the activities of the Melghat honey samples against the gram negative species *Escherichia coli.* Among the gram-positive species, three out of the four honey samples, i.e.. samples H_1, H_2, and H_3, have shown their maximum potential against the species *B. cereus*. While for the remaining honey sample, i.e., sample four H_4, it is in the second position. Thus, the Melghat honey samples have shown their highest potential against *B. cereus* among the gram negative bacterial species selected for the examination.

Table 1. Antibacterial activities against gram-positive bacteria

Sr. No.	honey samples	zone of inhibition		
		Staphylococcus aureus	*Bacillus subtilis*	*Bacillus cereus*
1	**Sample 1 (H_1)**	11 mm	13 mm	16 mm
2	**Sample 2 (H_2)**	14 mm	12 mm	15 mm
3	**Sample 3 (H_3)**	12 mm	12 mm	14 mm
4	**Sample 4 (H_4)**	15 mm	12 mm	12 mm

Table 2. Antibacterial activities against gram-negative bacteria

Sr. No.	honey samples	zone of inhibition		
		Escherichia coli	*Salmonella typhi*	*Pseudomonas fluorescence*
1	**Sample 1 (H_1)**	—	14 mm	12 mm
2	**Sample 2 (H_2)**	—	16 mm	12 mm
3	**Sample 3 (H_3)**	—	17 mm	14 mm
4	**Sample 4 (H_4)**	—	16 mm	13 mm

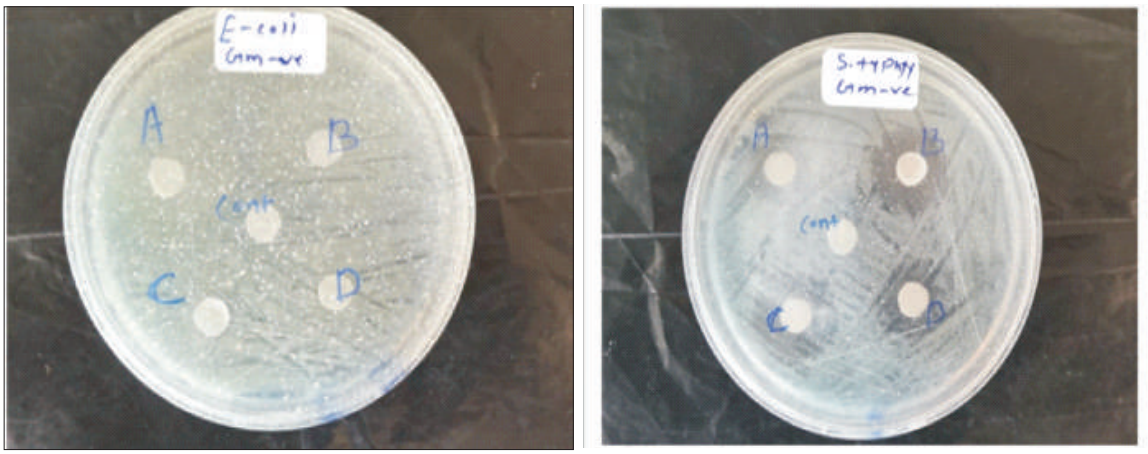


Figure 1. Zones of inhibition against *E. coli* and *S. typhi*

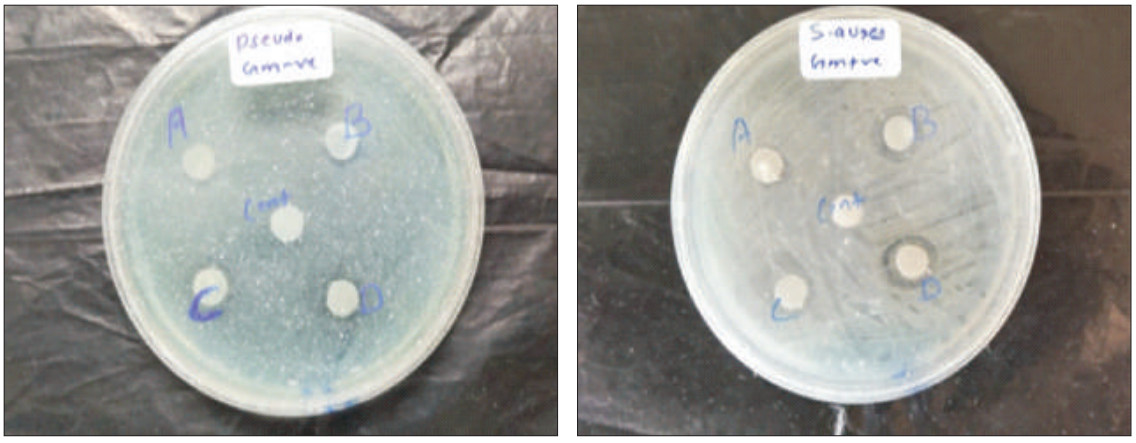


Figure 2. Zones of inhibition against *P. fluorescence* and *S. aureus*

Thus, the Melghat honey samples showed their prospective against five bacterial strains out of the six species that were selected for the experimental work. The zones of inhibition were of significant diameter, which might make this honey a spectacular natural antibiotic with no side effects. It was revealed that natural and unheated honey have comparably excellent potency against pathogenic bacteria (Mandal and Mandal, 2011). Tambekar and Rathod (2007) studied the antibacterial potential of Melghat and other branded honeys against the human pathogens *S. aureus, S. typhy, S. epidermidis, E. aeruginous, P. vulgaris, E. coli, Ps. aeruginosa,* and *K. pneumoniae*. It was reported that Melghat honey was found more effective against all the pathogens than the branded honey. The Melghat honeys, being wild, are the most natural and might be useful for therapeutic applications.

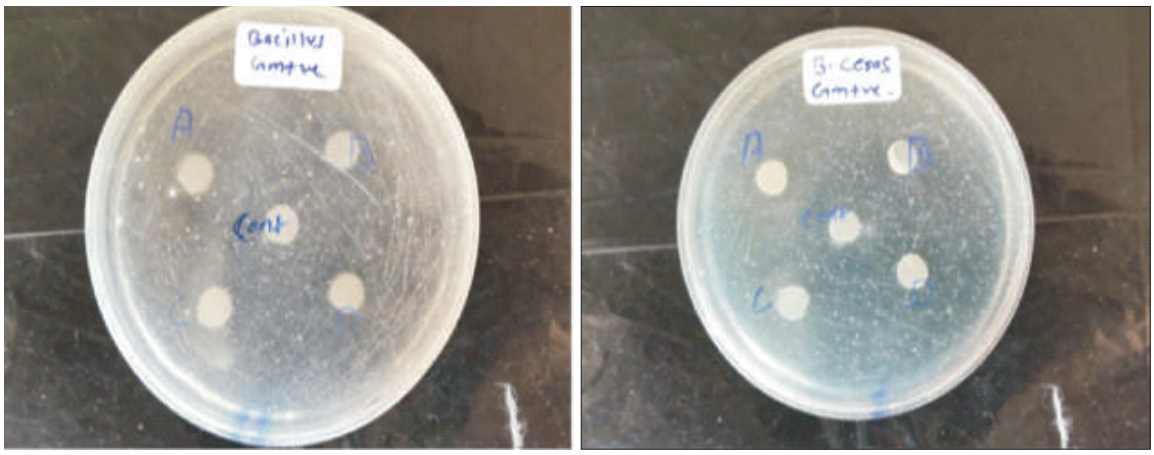


Figure 3. Zones of inhibition against *B. subtilis* and *B. cereus*

Kalidasan *et al.* (2017) evaluated the antibacterial potential of three varieties of honey, *viz*., Kombu honey, Malan honey, and commercial honey, against some bacterial species and obtained the zones of inhibition for *S. aureus* (34, 26, and 22 mm), *M. luteus* (30, 23, and 20 mm), *A. baumani* (22, 17, and 17 mm), *P. fluorescens* (23, 21, and 18 mm), *S. flexneri* (25, 22, and 19 mm), *P. mirabilis* (24, 20, and 15 mm), *E. coli* (28,19,and 17 mm), *K. pneumonia* (26, 18, and 16 mm), *S. typhi* (24, 21, and 19 mm), and *B. cereus* (32, 23, and 21 mm). In another study by Mandal and Mandal (2011), the honey samples under examination had shown their potential against *E. coli* (12-24 mm), *S. typhi* (0-20 mm), *S. aureus* (20-21 mm), and *P. fluorescence* (15-16 mm).

With the exception of *E. coli*, the results by Mohapatra *et al.* (2011) and Chauhan *et al.* (2010) were found to be analogous with the current work. Mohapatra studied the antibacterial activities of raw and processed honeys and got the zones against *E. coli* (16.14-28.49 mm), *S. typhy* (31.85-37.94 mm), *P. fluorescence* (13.09-35.95 mm), *S. aures* (8.58-11.54 mm), *B. subtilis* (7.25-11.19 mm), and *B. cereus* (6.94-23.7 mm). While Chauhan got the data against *E. coli* (14.0-29.4 mm), *S. typhy* (29.47-38.12), *P. aeruginosa* (13.09-35.95 mm), *S. aureus* (8.9-10.0 mm), *B. subtilis* (7.25-11.19 mm), and *B. cereus* (6.94-12.83 mm).

The application of honey as an antimicrobial agent for the infections found its roots in the prehistoric periods. The broad continuum of microbial species is restrained by honey. The differences in the activities of honey against the various bacteria may be the consequence of the effects of its heaps of physical and chemical properties. The mechanism of the antibacterial potential of honey was not understood clearly, but there were many factors that could be attributed to its splendid performance against a range of microorganisms. The physical and the above chemical factors are reported to be important for the properties of honey. The high osmotic pressure exerted due to the high sugar content disables the bacterial cells from growing. The water is squeezed out of their cells that brings the bacterial cells towards death. Due to the high amount of sugar, the viscosity of honey is elevated, causing the formation of a layer to protect the infected area from the septic bacteria. The high acidity (low pH) of honey is also responsible for its inhibitory effect against bacteria (Harun *et al*., 2017; Almasaudi *et al*., 2017).

Abeshu and Gelata (2016) reported that the formation of hydrogen peroxide due to the effect of glucose oxidase, an enzyme, is one of the most prominent parameters reported by most of the researchers behind the antibacterial property of honey. It is the byproduct of the synthesis of gluconic acid from glucose that acts as a destroying agent. The accumulation of H_2O_2 depends on the age of the honey, the effect of heating, and the floral origin. Another reason reported for the antibacterial properties of honey is the presence of 'inhibine', which may be sensitive to heat and light. They again added that the hydrogen peroxide in honey gets activated on dilution with body fluids and acts as an antibacterial agent.

According to Zainol *et al.* (2013), phenolic compounds and carbohydrates, the products of Maillard reactions, some proteins, and other compounds like peptides, methylglyoxal, etc., are also responsible for the antibacterial potential of honey. It is revealed that besides hydrogen peroxide, various non-peroxide components mentioned above, as well as methyl syringate and some unidentified compounds, showed antibacterial activities. Saranraj and Sivasakthi (2018) have supported the theory of defensins and the role of peptides in the antimicrobial mechanism. He elaborated that the peptides disrupt the membrane of microorganisms and carry out the depolarization of the inner membrane that leads to the reduction of cytoplasmic ATP. This hurdles the respiration of the bacterial cell, causing its death. Tambekar and Rathod (2007) suggested that the redox potential of vitamin C in honey plays a key role in its antibacterial activity.

Almost all the civilizations, traditions, and generations of the ancient as well as modern eras accepted the use of honey as a food and medicine due to its numerous beneficial properties, including antimicrobial potency. Honey not only shows its inhibitory effect against bacteria but also against fungus, viruses, and others. Many researchers supported this claim and revealed various possible mechanisms of honey's antimicrobial action (Israili, 2014; De-melo *et al*., 2017; Szweda, 2017).

Six types of bacteria were used for the experiment to detect the antibacterial potential of Melghat honey samples. It was concluded that all the honey samples showed their activities against almost all the bacterial species. The highest activity was observed against the gram-negative bacterial species *Salmonella typhi*. Surprisingly, it was observed that no honey sample showed its activity against the gram-negative bacteria *Escherichia coli*. Among the gram-positive species, three out of the four honey samples have shown their maximum potential against the species *Bacillus cereus*. The zones of inhibition were of significant diameter, which might make these honeys a spectacular natural antibiotic with no side effects.

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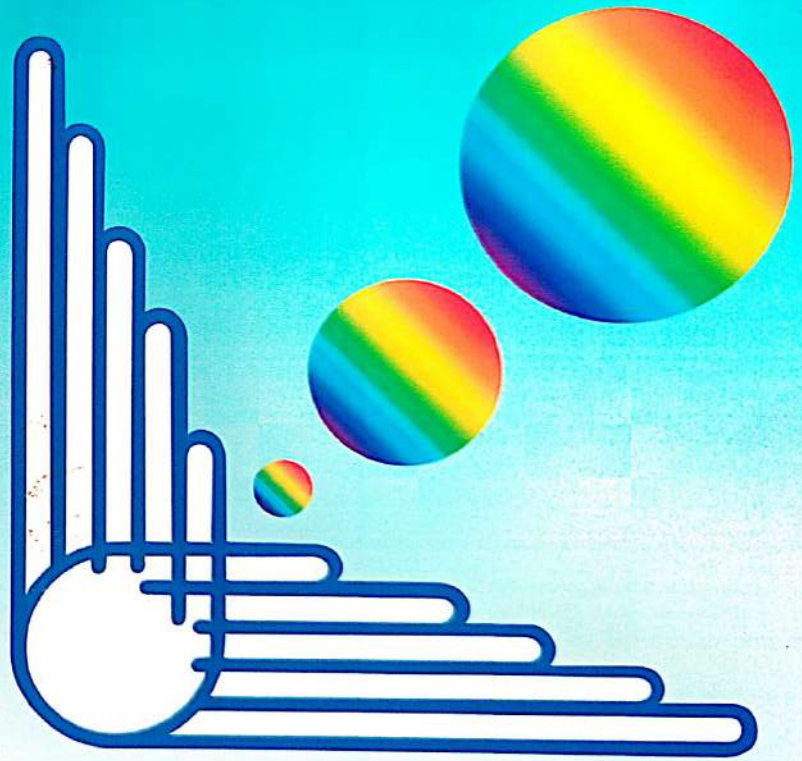
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Index

Sr. No.	Contents	Page No.
१.	यवतमाळ जिल्ह्यातील गळीत धान्य व तंतू पिके यांच्या पीक केंद्रीकरणाचा अभ्यास २०२२-२३ – डॉ. वैशाली बिजवे, – डॉ. सुमेध वरघट	१-९
२.	**Education in India: Journey from Past to Present** - Shri. Dayanand Sitaram Mokal	१०—१५
३.	बोधी ज्ञान प्राप्ती करिता दहा पारमितांचे पालन आवश्यक – प्रा.डॉ.मुकेश भा. सरदार	१६-२१

An International Indexed, Refereed, Peer Reviewed, Interdisciplinary, Multilingual, Multisubject Monthly Research Journal
Vol. X, Issue IV, April 2024
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३. बोधी ज्ञान प्राप्ती करिता दहा पारमितांचे पालन आवश्यक

प्रा.डॉ.मुकेश भा. सरदार
कला, विज्ञान व वाणिज्य महाविद्यालय चिखलदरा
जिल्हा अमरावती.४४४८०७

प्रस्तावना :-

भुकेचा प्रश्न सुटल्यानंतर माणूस मेंदूचा विचार करायला लागतो. मानसिक भूक ही पोटाच्या भुकेपेक्षाही मोठी आहे. मात्र त्याकडे बरेचदा मनुष्य प्राणी दुर्लक्ष करतो. त्यामुळे आळस, अज्ञान, लोभ द्वेष हे गुण त्यांच्या ठिकाणी उत्पन्न होतात. त्यामुळे त्यांचे चित्त अकुशल होते. त्यामुळे जीवनाचा अंत ही वाईटच होतो. हे ओळखून शहाणा माणूस अकुशल चित्ता पासून अलिप्त राहतो. चित्त कुशल बनविण्याचा प्रयत्न करतो .हा प्रयत्न दहा पारमितांचे पालन केल्याशिवाय पूर्ण होत नाही.

दहा पार मितांचे पालन करणे म्हणजे बोधी ज्ञान प्राप्त करण्याचा प्रयत्न होय. बोधी म्हणजे लोककल्याणाच्या तत्त्वाचे ज्ञान .त्या ज्ञानासाठी जो सत्व म्हणजे प्राणी सतत प्रयत्न करतो तो बोधिसत्व. पारमिता म्हणजे पारंगतता, पारमिता हा शब्दाचा अर्थ होतो पूर्णतः .पाली भाषेत याला पारमी म्हणतात. भगवान बुद्धांनी जीवनभर ह्या पारमितांचा अभ्यास केला म्हणून मानव जाती पुढे हा सर्वोत्तम आदर्श आहे.

चर्यापिटकात दहा पारमितांचे वर्णन जातकापेक्षा विशेष अलग शैली आहे. ती वाचल्यास पारमिता पूर्ण करण्याची प्रेरणा मिळते. भगवान गौतम बुद्ध प्रति सन्मान आणि गौरव निर्माण होतो. जगात दुःख विमुक्त होण्याची भावना जागृत होते. कठीणात कठीण कार्य करण्याचे, विपत्ती सहन करण्याचे तसेच सुखदुःखात एक समान होऊन राहण्याची भावना

An International Indexed, Refereed, Peer Reviewed, Interdisciplinary, Multilingual, Multisubject Monthly Research Journal
Vol. X, Issue IV, April 2024
ISSN : 2395-759X

निर्माण होते. ह्यात आकर्षण ,दया, सहिष्णुता, क्षमा, त्याग, ओजस्विता ओढ आणि उत्साह आहे. ज्यामुळे मनुष्य उन्नतीच्या शिखराकडे वाटचाल करीत राहण्याचा प्रयत्न करण्यासाठी प्रेरित होतो. (सुत्तपिटक).पेज नं 253, 254 ,255.) दान, शील, नैष्कर्म, प्रज्ञा, वीर्य, शांती, सत्य, अधिष्ठान, मैत्री, उपेक्षा, बीजरूपाने हे दहा गुण सर्व प्राण्यांमध्ये आहेतच. परंतु त्यांचा जे विकास करतात तेच बोधिसत्व होतात. तेव्हा अशा सदगुणांची हेडसांड न करता या पारमिता संपादनाचा सुज्ञ व्यक्तींनी सतत प्रयत्न करायला पाहिजे.

१) दान पारमिता: -

' तथागत भगवान बुद्ध म्हणतात, लोभ ह्या एका वस्तूला सोडा मी तुमची अनागामी होण्याची शाश्वती देतो. ज्या लोभामुळे लोभी होऊन प्राणी दुर्गतीला प्राप्त होतात .त्या लोकास योगी चांगल्या प्रकारे समजतात. आणि त्याचा त्याग करतात. लोभ हे पापाचे मूळ असल्यामुळे पापी चित्ताचा माणूस हिंसा करते. म्हणून दान पारमिता तथागतांनी सांगितली आहे. प्रथमतः तुम्ही गोरगरिबांना व आंधळ्या पांगळ्यांना पै पैसा दान करा. दानाने तुमच्या मनात कोमल दया उत्पन्न होऊन तुमची उन्नती करील .व तुम्हास बोधी मार्गाच्या पहिल्या पायरीजवळ आणील. लहानपणापासूनच दान करण्याची सवय लावून घेतल्यास दुसऱ्यासाठी स्वतःची धनसंपत्तीच काय तर स्वतःच्या शरीराचे देखील बलिदान द्यावयास तयार असतो .अशाच व्यक्तीला दानी समजल्या जाते .असे श्रेष्ठ लोक भवाचा सागर पार करून जात असतात.

२) शील पारमिता:-

तुम्ही दानधर्म पुष्कळ केला. किंबहुना आपला प्राणही लोककल्याणासाठी देण्यास तयार झाला. पण तुमचे शील निर्मळ नसेल तर सन्मार्गात तुमची उन्नती होणार नाही. जीव हिंसेपासून म्हणजेच मनुष्य हत्ये

पासून दूर राहणे, चोरी न करणे, व्यभिचार न करणे, खोटे न बोलणे, मादक द्रव्याचे सेवन न करणे, त्याचे समर्थन न करणे, दुसऱ्याला पण तसेच करण्यास प्रेरणा न देणे, अशा व्यक्तीला शीलवान व्यक्ती म्हणून समजल्या जाते. थोडक्यात अकुशल कर्माचा त्याग करून कुशल कर्मे जो करीत राहतो, तो आकाशातील ताऱ्यासारखा समाजात आपल्या तेजाने चमकत राहतो .

३) नैष्कर्म्य पारमिता :-

एकांताची गोडी धरणे व त्यात पूर्णत्व संपादने यालाच नैष्कर्म्य पारमिता असे म्हणतात. नैष्कर्म्य म्हणजे संसारिक काम भोगाचा त्याग करणे होय . म्हणून अनित्य भावना करून पारमिता पूर्ण करता येते. त्यासाठी सौंदर्यावर प्रेम तर करावेच पण त्याचबरोबर कुरूपतेवर देखील तेवढेच प्रेम करता आले पाहिजे. अशा व्यक्ती नैष्कर्म्य पारमिता पूर्ण करू शकतो.

४) प्रज्ञा पारमिता:

एकांत वासाच्या योगे तुम्ही ज्ञान मिळवण्यास समर्थ झाले पाहिजे. लोकोपयोगी ज्ञान मिळवून ते पूर्णत्वाला नेणे याला प्रज्ञापारमिता म्हणतात. प्रज्ञा म्हणजे लोक कल्याणाची तीव्र अपेक्षा धरून मिळवलेले सात्विक ज्ञान. ते मिळवण्यासाठी तुम्हाला लहानपणापासूनच शील आणि समाधी याचा अभ्यास केला पाहिजे. शीला संपन्न ,समाधी संपन्न, व्यक्तीला सम्यक दृष्टी असलेला व्यक्ती म्हणतात. चार ज्ञान म्हणजे श्रोता संपन्न, सकृतागामी, अनागामी आणि अरंहन्त होण्यासाठी प्रज्ञा प्राप्त असणे गरजेचे आहे. प्रज्ञावंत हा मागील हजारो जन्माच्या आणि पुढील हजारो जन्माचा इतिहास जाणत असतो. प्रज्ञावंताला समाजात श्रेष्ठ आर्य व्यक्ती समजल्या जाते.

५) वीर्य पारमिता:-

An International Indexed, Refereed, Peer Reviewed, Interdisciplinary, Multilingual, Multisubject Monthly Research Journal
Vol. X, Issue IV, April 2024
ISSN 2395-759X

वीर्य म्हणजे सम्यक प्रयत्न. जो उत्तम संकल्प केला त्यास पूर्ण करावयास संपूर्ण सामर्थ्यानिशी प्रयत्न करणे आणि त्यास पूर्ण केल्याशिवाय मागे वळून न पाहणे. वीर्य म्हणजे सत्कर्म करण्याचा उत्साह. त्यात पारंगत होणे याला वीर्य पारमिता म्हणतात. बोधिसत्व ही तुमच्या आमच्या पेक्षाही दुर्लब प्राणी होते. परंतु केवळ आपल्या सदूद्योगाने त्यांनी बोधी मिळवली. तुम्ही तर सर्व अवयव संपन्न आहात. आणि आपले हिताहित जाणण्याचे शहाणपण तुमच्या अंगी आहे .मग असल्या हलक्या सलक्या खाली खुशालीत वेळ न दडवता स्वतःच्या उन्नतीचा सतत उत्साह वाढवीत राहणे यातच खरे शहाणपण आहे.

६) शांती पारमिता:-

शांती म्हणजे क्षमाशीलता. शांती म्हणजे सहनशीलता, कुरूप - सुरूप यांची घृणा न करणे, घृणाच्या मोबदल्यात क्षमाशीलता दाखविणे, संपूर्ण इंद्रिय शांत करण्याची साधना म्हणजे शांती होय. लोभ ,द्वेष आणि मोहाचे समुळ उच्चाटन करण्यासाठी शांतीपारमिता शिवाय दुसरी पारमिता नाही. शुराला कधीच क्रोध येत नसतो. म्हणून खरे सौंदर्य संपादण्यासाठी तुम्ही शांतीचा अभ्यास केला पाहिजे .राग आपोआप येत असतो. पण क्षमा प्रयत्नाने संपादावी लागते. म्हणून क्षमा करण्याची संधी तुम्ही फुकट दळवता कामा नये.

७) सत्य पारमिता:-

शांतीला सत्याची जोड दिली नाही तर तिचा विपर्यास हाजी हाजीत करण्यात होईल. वाटेल तो प्रसंग येवो सत्याला सोडून तिड मात्र ही इकडे तिकडे जाणार नाही. असा निश्चय केला पाहिजे. सत्यासाठी एकटेच वाघासारखे चालत गेले पाहिजे. सम्यक वाणीने कोणाचेही मन न दुखविता सत्याचा अविष्कार केला पाहिजे. सत्यवादी माणसाची समाजात .आणि कुटुंबात मान सन्मानाची जागा असते. सत्यवादी मनुष्य हा विश्वासास पात्र

असतो. समाज त्याच्यावर विश्वास ठेवतो. त्यामुळे लोककल्याणाची कामे सत्यवादी माणसामुळे होत असतात. सत्य म्हणजे कितीही वाईट प्रसंग आला तरी खोटे न बोलणे होय.

८) अधिष्ठान पारमिता: –

अधिष्ठान म्हणजे आपल्या उद्देशापर्यंत पोहोचविण्याचा दृढ निश्चय होय. ध्यानाशिवाय ज्ञान नाही. म्हणजे समाधी भावना प्राप्त करण्यासाठी अधिष्ठानाची खूप आवश्यकता असते. लहान-सहान कर्मातही तुमचे बेत तंतोतंत पाळण्याचा अभ्यास तुम्ही केला पाहिजे. विचारपूर्वक कर्तव्य पार पाडताना कितीही विघ्ने आली तरी ते पार पाडण्याचे सामर्थ्य तुम्ही संपादिले पाहिजे.

९) मैत्री पारमिता: –

मैत्री म्हणजे सर्व प्राण्यांविषयी सुखाची कामना करणे. मित्रासाठीच नव्हे तर शत्रू विषयी देखील भातृ भावना ठेवणे होय. भेदभाव न ठेवता सर्वांवर सारखे प्रेम करणे यालाच मैत्री म्हणतात. देश परत्वे मनुष्य जाती भिन्न असले तरी तिची सुखदुःखे एक आहेत. सतत अभ्यासाने सगळ्या जगावर मैत्री करण्याची सवय लावून घेतली पाहिजे. पशुपक्षादी प्राणी माझे सख्खे आहेत. माझ्यावर प्रेम करतात. व मी त्यांच्यावर प्रेम करतो. अशी भावना केली पाहिजे. त्यामुळे तुम्ही निर्भय व्हाल व तुम्हाला दृष्ट स्वप्ने पडणार नाहीत.

१०) उपेक्षा पारमिता: –

उपेक्षा म्हणजे अनासक्ती. याचा अर्थ इतरांच्या सुखदुःखाविषयी निरपेक्ष भाव. नव्हे,ही चित्ताची अवस्था आहे. ज्यात प्रिय अप्रिय काहीही नसते. फळ काहीही असो त्याविषयी निरपेक्ष राहून साधना करण्यात मग्न राहणे यालाच उपेक्षा म्हणतात.

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ISSN : 2395-759X

आपण दुसऱ्याचे कल्याण करण्याचा प्रयत्न केला पाहिजे. अशावेळी कोणी विरोध केला तर त्याची उपेक्षा केली पाहिजे. एखाद्या व्यक्ती आपल्या विरोधी बोलतो, लिहितो अशावेळी त्याला उत्तर न देता त्याची उपेक्षा केली पाहिजे .लोककल्याणाच्या उद्योगाला आपण लागलो की, असे अनेक प्रसंग येतील त्या प्रसंगी उपेक्षा पारमिताचा अभ्यास करावा. थोडक्यात या छोट्याशा लेखाने दहा पार मितांचा अभ्यास करण्याची गोडी सुजाण वाचकास लागल्यास माझ्या प्रयत्नाचे सार्थक झाले असे मी समजेन.

संदर्भ ग्रंथ:–

१) मज्झिमनिकाय निकाय–३ लेखक मा.श. मोरे प्रकाशक उषा वाघ सुगावा प्रकाशन ५६२ सदाशिव पेठ, पुणे 30 पेज नंबर –६.
२) बौद्ध धम्म जिज्ञासा संकलिका :–कीर्ती पाटील पारमिता प्रकाशन नागपूर. पेज नंबर ६६,६७.
३) जातक कथा, भाग १ ते ३ लेखक धर्मानंद कोसंबी साकेत प्रकाशन, प्रायव्हेट लिमिटेड छत्रपती संभाजी नगर. ४३१००५ पेज नंबर ६,७,८,९.
४) भगवान बुद्ध. आचार्य धर्मानंद कोसंबी कौशल्य प्रकाशन, औरंगाबाद. ४३१००३ पेज नंबर १२०.

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- PHYSICS
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राममंदीर के पास, पेठ पुरा, हिवरखेड (रुप.), ता. तेल्हारा, जि. अकोला, महाराष्ट्र - ४४४९०३ से प्रकाशित

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Index

Sr. No. **Contents** **Page No.**

1. **Challenges of 21st Century Education**
   - Prof. Mayur Bandu Lahane 1-6

2. **Mathematics in the Lower Primary Years: A Research based Perspective on Curricula and Teaching Practice**
   - Dayanand Sitaram Mokal 7-23

3. बाल कामगार प्रथाचे विविध दुष्परिणाम व उपाययोजना
   – प्रा. दिगंबरकुमार लांडगे २४–२८

४. डॉ. भाऊ लोखंडे यांचा मराठी साहित्याला समृद्ध करणारा थेरगाथा हा अप्रतिम ग्रंथ
   – प्रा.डॉ.मुकेश भा. सरदार २९ –३३

होणाऱ्या दुष्परिणामाविषयी माहिती द्यावी व कुटुंबाचा आकार नियंत्रणात ठेवण्याचे कायदे सांगावे व समाजामध्ये या समस्येविषयी जनजागृती करावी.

सारांश

२००१ च्या जनगणनेच्या तुलनेमध्ये २०११ मध्ये बाल कामगारांची संख्या कमी झाली. परंतु ही समस्या पूर्णपणे नष्ट झाली नाही. ज्या योजनांमुळे ही संख्या कमी झाली त्या योजना अधिक प्रभाविपणे राबविल्यास ही संख्या अधिक प्रमाणात कमी होण्यास मदत होते. बाल कामगार विविध कारणामुळे काम करत असतात परंतु त्यामध्ये सर्वात महत्वाचे कारण म्हणजे आर्थिक कारण आहे. आर्थिक परिस्थिती खालावलेली असल्यामुळेच जास्तीत जास्त मुले कामाकडे वळतात. आजचे बालक देशाचे भवितव्य आहेत, ती देशाची एक अमूल्य संपत्ती आहे. मुलांच्या विकासावरच राष्ट्राचा विकास अवलंबुन असतो. यासाठी मुलांना कामाला न पाठवता शाळेमध्ये पाठविण्याची गरज आहे. परंतु अनेक मुले काम करतांना दिसून येतात. याकडे सर्वजन दुर्लक्ष करतात बाल कामगारांचे कामादरम्यान शोषण केल्या जाते. बालकाकडून शारीरिक कष्टाची कामे करुन घेणे म्हणजे माणुसकीला काळीमा फासणारी बाब आहे. भारत सरकारने बाल कामगारांची प्रथा नष्ट करण्यासाठी अनेक घटनात्मक तरतूदी आणि कायदे केले तरी ही प्रथा दिसून येते. ही प्रथा नष्ट करण्यासाठी कायद्याच्या योग्य अंमलबजावणीची व यासाठी सर्व समाजघटकांनी प्रयत्न करण्याची गरज आहे.

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कला, विज्ञान व वाणिज्य महाविद्यालय चिखलदरा
जिल्हा अमरावती.४४४८०७

बहुजन साहित्य प्रसार केंद्र नागपूर येथून प्रकाशित २४ ऑक्टोबर १९८४ बुधाब्द २५२८ यावर्षी सुजित मुरमाडे यांनी प्रकाशित केला. प्रा. डॉ. रत्नामाला लोखंडे यांना या ग्रंथाचे सर्वाधिकार प्रदान करण्यात आले. याची द्वितीय आवृत्ती १४ ऑक्टोबर २०१९ बुद्धाद्ध २५६३ ला प्रकाशित करण्यात आली. या ग्रंथाचे मुखपृष्ठ शशी भोवते यांनी तयार केले असून ग्रंथाची अक्षर जुळवणी सिवली ग्राफिक्स नागपूर तर मुद्रण वंश क्रिएशन नागपूर येथून करण्यात आले. या ग्रंथाची किंमत अत्यल्प शंभर रुपये असून हा ग्रंथ पु. ल. देशपांडे व डॉ.भदंत आनंद कौशल्यायन यांना समर्पित करण्यात आला. या पुस्तकाचा आकार २१बाय १५ चा असून एकूण १७१पानांचा हा ग्रंथ आहे.

या ग्रंथाचे मुखपृष्ठ बोलके असून पाहता क्षणी डोळ्यात भरणारे आहे. सम्यक दृष्टी प्राप्त झालेल्या भिक्खूला मंगल मैत्री देत आहेत. करूनेचा वर्षाव तेथे बसलेल्या आठ भिक्षूवर सम्यक संबुद्ध करीत आहेत. असे दाखविण्याचे प्रयोजन असे असावे की ,सामगाम सुत्तात १०४ सांगितल्याप्रमाणे बोधिप्राप्तीसाठी चार सती पठाण चार सम्यक प्रधान चार रिद्धीपाद, पाच इंद्रिय, पाच बल, सात बोधांग आणि आर्य अष्टांगिक मार्ग या सदतीस बोधिपक्षीय धर्माचा उल्लेख सामगम सुत्तातात 104 आणि किंती सुत्तात 103 मध्ये केला गेला आहे. म्हणजेच आर्य अष्टांगिक मार्गाद्वारे बोधी किंवा निर्वाण प्राप्त करता येतो. त्यासाठी सम्यक दृष्टी,

सम्यक संकल्प ,सम्यक वाणी, सम्यक कर्मांत,सम्यक आजविका, सम्यक व्यायाम ,सम्यक स्मृतीआणि संम्यक समाधी असे हे मानवी विकासाचे आठ अंग आहेत. म्हणून आठ भिख्खू दाखविण्यात आले असावे. आणि या आठ भिख्खूना सम्यक संम्बुद्ध उपदेश देत आहेत. त्यांच्याकडून आनापान सती आणि विपश्यना कर्म करून घेण्यात येत आहे असे दाखविले आहे मलपुष्ठावर प्रा. डॉ. भाऊ लोखंडे यांचा डोळ्याला दिपवून टाकणारा परिचय देण्यात आला आहे.

थेरगाथेत प्रवेश करण्यापूर्वी मध्ययुगीन भारतात अनेक विविध संतांनी आपल्या वाणी व वर्तनातून समाजाला भक्ती, शांती व समतेचा उपदेश दिला त्यातील संत ज्ञानेश्वर, नामदेव, तुकाराम, एकनाथ, चोखामेळा, रविदास, कबीर, नानकदेव, संत मीराबाई बहिणाबाई जनाबाई ही काही अतिप्रसिद्ध नावे आहेत. यांचे अंत:करण चित्त मलापासून मुक्त झाल्यामुळे ते अध्यात्मिक शांतीला प्राप्त झाले. त्यांच्या मनातील तृष्णा शांत झाली म्हणून ते संत या संज्ञेला प्राप्त झाले. अशा या जीवन मुक्त स्थविरांनी निर्वाणप्राप्तीनंतर उद्भवणाऱ्या उल्हास वा हर्षतिरेकाच्या अवस्थेत जे सहज हर्षउद्गार आपल्या वाणी द्वारे उच्चारले त्यांना उदान असे म्हणतात. आणि या थेरांच्या उदानांना गाथांचे संकलन थेरगाथा या ग्रंथात केलेले आहे." भोगावरी आम्ही घातला पाषाण मरणाही मरण आणियले "या संत तुकोबाच्या मुक्त अवस्थेचीच या अवस्थेची तुलना शक्य आहे. विमुक्तिसूख आणि तृष्णा नाशाचा परमानंद अवस्थेत सहज स्फुरलेल्या आणि पोटातून सहज प्रस्थापित झालेल्या अशा अनेक विविध गाथा नी ओतप्रोत भरलेला हा ग्रंथ आहे.

थेरगाथा या ग्रंथाची भाषा ओघवती, सौंदर्यवती, लावण्यवती सारखी आहे. उदाहरणार्थ _ "फुलांचा रंग व गंधाला धक्का न लागू देता रसग्रहण करणाऱ्या भ्रमराप्रमाणे निरूपद्रवी बनवून समाजात सेवकाप्रमाणे

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वावरतो केवळ उदरनिर्वाह उद्देश भिक्षांना ग्रहण करून तो जनसामान्याला सदाचार व सद्गम्माचे प्रज्ञाचे अधिकाधिक शिक्षण देऊन समाजाची बौद्धिक आणि नैतिक भूक भागवीत असतो. किंवा निरागससृष्टीचे सौंदर्य थेरांच्या चित्तवृत्तीला प्रसन्न आणि पवित्र बनवितात अशा वातावरणाने भारावून अनुभवलेल्या परमानंदाचे वर्णन करीत भूतनामक स्थवीर म्हणतात," आकाशात मेघांची दुदुंभी गरजत आहे,पक्षांचा संपूर्ण मार्ग जलधारांनी भिजलेला आहे. नदी काठावरील सुंदर झाडे चित्र विचित्र वन फुलांनी लगडलेली आहेत. निर्जन जंगलामध्ये हत्तीचा चित्कार निनादत आहे. रिमझिम रिमझिम पाऊस पडतो आहे ."अशा रमणीय वातावरणात नदीकाठावर किंवा पर्वत गृहे मध्ये ध्यान करीत बसलेल्या भिखूला त्यापेक्षा परमानंदाचा दुसरा कोणता क्षण असणार? भगवंतांना आपल्या जन्मभूमीत येण्याचे निमंत्रण देत काळुबाई स्थवीर झाडांचे काय सुंदर वर्णन करतात, ते पहा "भन्ते आता सर्व झाडे निखाऱ्याप्रमाणे लाल भडक असलेल्या पळस फुलांनी सजलेली आहेत. जणू फळांच्या अपेक्षित पानांचा त्याग करून ती झाडे पेटत्या मशालीप्रमाणे शोभून दिसत आहेत. तळपुट स्थवीर,पावसात भिजण्याची आपली इच्छा व्यक्त करीत म्हणतात," ऋषीमुनी ज्या मार्गवरून वनात चालले गेले त्या मार्गाचे अनुसरण करणारे माझे जीवन वर्षा ऋतूची पावसाची पहिली सर भिजवून चिंब चिंब करीत आहे". पावसात भिजण्याची केवढी उत्कंठा आहे भंते काश्यप रम्य पर्वताचे काय बहारदार वर्णन करतात, ते पहा "जेथे करेरी फुलांच्या माळा अंथरलेले भूप्रदेश आहेत, निळ्या मेघाप्रमाणे थंड आणि स्वच्छ जलाशय आहेत. इंद्रधनुष्यांनी जे व्यापलेले आहेत. पावस पाण्याने जे प्रफुलित झालेले आहेत. जे नानाविध पक्षांच्या थव्यांनी गजबजलेले आहेत. हे हरींनाच्या कळपांणी भरलेले आहेत आणि हत्तीचा चित्कार आणि मोरांच्या केकार याचा पडसाद निनादत आहेत." असे ते रमणीय

पर्वत मला फारच आवडतात. अशी अनेक उदाहरणे देता येतील की , जेथे स्थवीर सृष्टी सौंदर्याने वेडावून गेले आहेत.

थेर गाथेत भगवंताच्या समतावादी मानव प्रीतीचा सोहळा पहावयास मिळतो. त्यांनी माणसाच्या जन्मा पेक्षा कर्माला अधिक महत्त्व दिले आहे. जन्माने नाहीतर कर्माने मनुष्य ब्राह्मण किंवा हीन ठरत असतो. हा बुद्धाचा सनातन सिद्धांत आहे.

भाऊ लोखंडे म्हणतात," मराठी संत साहित्यात संत रामदासाचे मनाचे श्लोक प्रसिद्ध आहेत." परंतु रामदासाच्या प्रत्येक शतके आधी बौद्ध संत स्थविरांनी मनाला उद्देशून आपले मनोगत थेर गाथेत अभिव्यक्त केले आहेत. हत्तीवान पुत्र विजीत सेन स्थवीर आपल्या अनावर मनाला ज्याचे मन "मन माझे नाव रे आवरिता" असे वर्णन रामदासांनी केले आहे. स्थवीर ताळपुट यांनी केले व भगवान बुद्ध म्हणतात चित्त माकडाप्रमाणे चंचल असून त्याला वश करणे कठीण आहे. हे चित्ता! तू माझा वारंवार विश्वासघात करतोस. परंतु मी आता भडकलेल्या हत्तीला वश करणाऱ्या अंकुश धारी हत्ती वाना प्रमाणे तुला वश व ताब्यात केल्याशिवाय राहणार नाही.

अशा ह्या ग्रंथाबद्दल अंगुलीमाल अहिंसक स्थवीरांच्या भाषेतच म्हणावेसे वाटते माझ्या शत्रूंनी ही धर्म कथा ऐकावी आणि बुद्ध शासनाप्रमाणे आचरण करावे. भारतीय संत साधनेची गंगोत्री असलेला थेरगाथा हा ग्रंथ तणावग्रस्त मानवी मनाला काही प्रमाणात निश्चित शांती प्रत आणि मार्गदर्शक ठरणार आहे. यातील अनुक्रमणिका एकूण 36 वर्गात असून बौद्ध धम्मात जे भिक्खू अरहंत होऊन गेले त्यांच्या व्यक्तिमत्त्वाचे आणि त्यांच्या उपदेशाचे हृदय गम्य असे वर्णन या ग्रंथात करण्यात आलेले आहे. जिज्ञासू वाचकांनी हा ग्रंथ एकदा नक्की अभ्यासावा असे लेखकाला मनापासून वाटते.

संदर्भ ग्रंथ

१) थेर गाथा लेखक भाऊ लोखंडे प्रकाशक सुजित मुरमाडे, बहुजन साहित्य प्रसार केंद्र नागपूर.
२) समाधी मार्ग लेखक आचार्य धर्मानंद कोसंबी, प्रकाश डॉक्टर अशोक गायकवाड कौशल्य प्रकाशन 11 सी ३/२४/०३ हडको औरंगाबाद.
३) ब्रह्मजालसूक्त लेखक प्राध्यापक डॉक्टर तुळजा डोंगरे प्रकाश नेहा प्रकाशन अशोक नगर नागपूर.
४) मराठी संत साहित्यावर बौद्ध धर्माचा प्रभाव लेखक डॉक्टर भाऊ लोखंडे प्रकाशक उषा वाघ सुगावा प्रकाशन ५६२ सदाशिव पेठ पुणे.४११०३०.

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Extraction of Bioactive Chemicals from *Solanum Viarum* Leaves and GC-MS Study

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Abstract: Approximately 1500 species make up the biggest genus in the Solanaceae family, Solanum, which is mostly found in tropical and subtropical parts of the world. Solanum has a large number of commercially significant plant species that are used as food, ornaments, and medicines. *Solanum viarum* Dunal is one of the numerous plants in the Solanaceae family. The primary chemical components of the plant include steroidal glycoside, alkaloids and also flavonoids, saponins, minerals etc. Medicinal uses exist for the plant's root, stem, fruit seeds, and flowers. The presence of phyto components in a plant determines its pharmacological characteristics. Literature survey reveals that *Solanum viarum* has been linked to a variety of pharmacological actions like antibacterial, antifungal, antipyretic, antioxidant, antianalgesic anticancer etc. In the present study, using a Soxhelt extractor, methanolic leaf extract of *Solanum viarum* Dunal was obtained which was then concentrated in a rotary evaporator. GC-MS study of the concentrated extract has been carried out. The study revealed the existence of total 44 chemicals, among which four major chemicals are 1,3,4,5-Tetrahydroxycyclohexanecarboxylic acid, 2-Hexadecen-1-ol, 3,7,11,15-Tetramethyl-, [R-[R*,R*-(E)]]- (T-Phytol) , Undecane, 2,4-Dimethyl- and But-3-en-1-yl 2-methylbutanoate.

KEYWORDS

Solanum viarum, Leaf extract, GC-MS Study

I. INTRODUCTION

The *Solanum viarum* Dunal also known as tropical soda apple is referred to as ‘Kanthakari’ in India. It is extensively distributed over central, south, north-west, and northeastern India [1]. A sharp, massive prickle covers the aerial portion of *Solanum viarum*, encompassing the stem, leaf, and petioles, including the calyx. *Solanum viarum* is an important medicinal plant in the medicine and pharmaceutical industries [2]. While most people are unaware of the plant *S. viarum*, a review of the literature reveals that it is used to treat cancer and Addison's disease, a chronic endocrine illness caused by insufficient steroidal hormone production by the adrenal gland [3]. In addition, it is used to treat leukemia, rheumatism, skin conditions, and persistent asthma. The chemical components of the plant are also utilized in the treatment of palsy, a condition in which the face's muscles momentarily lose their power and become paralyzed. The chemical constituents like solasodine and other glycoalkaloid chemical components are utilized in the manufacture of several steroidal compounds, including cortisone [4]. As other members of the *Solanaceae* family also contain steroidal alkaloids, review of literature suggests that *S. viarum* is a suitable source for the commercial manufacture of solasodine in India [5]. Considering the medicinal importance of *Solanum viarum*, an attempt has been made to undertake a phytochemical study of leaf extract of *Solanum viarum*. Furthermore, the phytochemical constituents were identified from methanolic extract of this plant by using gas chromatography-mass spectrometry (GC-MS) analysis.

II. MATERIALS AND METHODS

Collection of Plant Material

The fresh leaves of *Solanum viarum* were collected in April 2023 from Melghat region, District Amravati, Maharashtra, India. This area lies at latitude 21.406°and longitude 77.319°. The plant was authenticated by botanist Dr.S.K Tippat, Department of Environmental Science, Smt. Narasamma Arts, Commerce and Science College, Amravati.

Preparation of Plant Extract

The leaves were rinsed with deionized water and gently blotted with paper towel to remove the water and subsequently dried over ambient temperature. The dried leaves then ground properly into powder. The dried powder sample was extracted at 65ºC in a Soxhlet apparatus by using methanol solvent. Extract was concentrated by gradually evaporating the solvent on rotary evaporator [6]. The concentrated extract was transferred in a sterile bottle and kept in a cool and dark place prior to analysis [7].

GC-MS Study of *Solanum viarum*

Gas Chromatography and Mass Spectroscopy:

A Shimadzu GC-MS, Model Number: QP2010S with column:ELITE-5MS, 30 meter length, 0.25 mm ID and 0.25 µm thickness was used for study having software GCMS Solutions. Low-resolution mass spectra were acquired at a resolving power of 1000 (20% height definition) and scanning from m/z 25 to m/z 700 at 0.3 seconds per scan with a 0.2 second inter-scan delay. High resolution mass spectra were acquired at a resolving power of 5000 (20% height definition) and scanning the magnet from m/z 65 to m/z 750 at 1 second per scan [8].

Identification of Chemical Constituents

Using a mass spectra library search NIST and Willey 8 and a comparison of the mass spectral and retention data with literature, the chemical constituents were identified based on retention index (RI). Without the use of a correction factor, the relative quantities of each component were determined using the GC peak area (FID response) [9, 10].

III. RESULTS AND DISCUSSION

The present study was carried out with methanolic extract of *Solanum viarum* leaves. Total 44 compounds were identified. The results are presented with the help of the Fig.1 and Table 1.

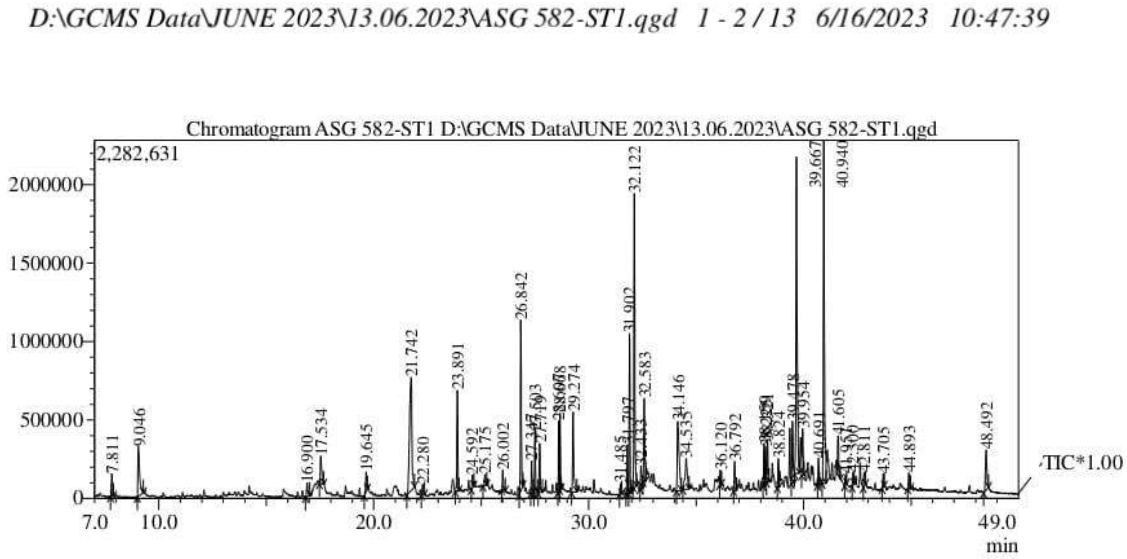


Fig.1: Gas chromatogram mass spectrum of leaf extract of *Solanum viarum*

Table 1: Compounds with % peak area

Peak#	R.Time	Area%	Height%	Name
1	7.811	0.76	0.82	Benzene, Nitro-
2	9.046	2.87	1.78	2-Pyrrolidinylmethanol
3	16.900	0.60	0.50	Dodecanal
4	17.534	1.34	1.00	Benzaldehyde, 2-hydroxy-6-methyl-
5	19.645	0.69	0.72	Benzenamine, 2,5-Dibromo-
6	21.742	9.05	4.06	1,3,4,5-Tetrahydroxycyclohexanecarboxylic acid #
7	22.280	0.34	0.39	Methanone, Diphenyl-
8	23.891	2.99	3.63	2,4,6-Tribromoaniline
9	24.592	0.47	0.46	4-((1E)-3-Hydroxy-1-propenyl)-2-methoxyphenol
10	25.175	0.42	0.41	2-Hydroxycyclopentadecanone #
11	26.002	0.61	0.72	Trans-2-undecenoic acid
12	26.842	4.99	6.15	Neophytadiene
13	27.347	0.88	1.16	3,7,11,15-Tetramethyl-2-hexadecen-1-ol
14	27.503	1.64	2.24	Tetradecanoic acid, 3-Hydroxy-, Methyl ester
15	27.719	1.49	1.77	3,7,11,15-Tetramethyl-2-hexadecen-1-ol
16	28.607	1.89	2.56	Hexadecanoic acid, Methyl ester
17	28.668	1.73	2.74	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, Methyl ester
18	29.274	2.98	2.89	9-Octadecenoic acid (z)-
19	31.485	0.30	0.39	Hexadecanoic acid, 3-Hydroxy-, Methyl ester
20	31.797	1.22	1.74	9,12-Octadecadienoic acid, Methyl ester
21	31.902	4.32	5.74	9,12,15-Octadecatrienoic acid, Methyl ester, (Z,Z,Z)-

22	32.122	8.53	10.52	2-Hexadecen-1-ol, 3,7,11,15-Tetramethyl-, [R-[R*,R*-(E)]]- (T-Phytol)
23	32.433	0.92	0.82	Heptadecanoic acid, 16-Methyl-, Methyl ester
24	32.583	2.87	2.99	9,12,15-Octadecatrienoic acid, (Z,Z,Z)-
25	34.146	4.49	2.50	Benzo[g]pteridine, 2,4-diamino-6,7,8,9-tetrahydro-7-methyl-
26	34.535	2.23	1.11	Nonane, 5-(1-Methylpropyl)-
27	36.120	0.46	0.53	Pentanoic acid, 4-methyl-2-oxo-, Methyl ester
28	36.792	0.97	1.06	4,4-Dimethyl octane
29	38.159	1.20	1.53	Nonane, 5-butyl-
30	38.225	0.68	0.98	Heptadecane, 7-Methyl-
31	38.321	1.26	1.49	Nonane, 5-butyl-
32	38.824	0.98	1.04	Hexadecanoic acid, 1-(Hydroxymethyl)-1,2-Ethanediyl ester
33	39.478	2.35	2.22	2,2-Dimethylpropanoic acid, 4-hexadecyl ester
34	39.667	12.25	11.37	Undecane, 2,4-Dimethyl-
35	39.954	1.59	1.67	9H-Xanthen-9-one, 3,6-dihydroxy-1,8-dimethyl-
36	40.691	0.75	0.97	2-Hexanone, 1,1,1-Trifluoro-
37	40.940	11.87	12.32	But-3-en-1-yl 2-methylbutanoate
38	41.605	0.93	1.10	8-Hydroxy-2,2,8-trimethyldeca-5,9-dien-3-one
39	41.951	0.35	0.38	9-Methyl-Z-10-pentadecen-1-ol
40	42.300	0.34	0.48	Terephthalic acid, 2-ethylhexyl undecyl ester
41	42.811	0.46	0.51	Octadecanoic Acid, 3-Hydroxy-, Methyl ester
42	43.705	0.39	0.50	Sulfurous acid, butyl hexyl ester
43	44.893	0.50	0.57	2,2,4-Trimethyl-3-(3,8,12,16-tetramethyl-heptadeca-3,7,11,15-tetraenyl)-cyclohexanol
44	48.492	2.00	1.46	Vitamin E
		100.00	100.00	

The result shows four major compounds found in the leaf extract. First major compound was 1,3,4,5-Tetrahydroxycyclohexanecarboxylic acid (9.05 % peak area) is a quinic acid (an astringent) used in synthesis of pharmaceuticals [11]. The second major compound was 2-Hexadecen-1-ol, 3,7,11,15-Tetramethyl-, [R-[R*,R*-(E)]]- (T-Phytol) (8.53% peak area). Phytols have found to be effective hypoglycemic agents [12]. Third major compound identified was Undecane, 2,4-Dimethyl- (12.25 % peak area) having anti-allergic and anti-inflammatory properties [13]. But-3-en-1-yl 2-methylbutanoate (11.87 % peak area) was the fourth major compound. The presence of biologically active compounds in leaf extract makes *Solanum viarum* an important medicinal plant. Major compounds have been presented in Table 2.

Table 2: Major chemical constituents with % peak area

Sr. No.	Retention Time	Name of Chemical Constituent	Molecular Formula	Molecular Weight	Peak Area %
1	21.742	1,3,4,5-Tetrahydroxycyclohexanecarboxylic acid	$C_7H_{12}O_6$	192.16	9.05
2	32.122	2-Hexadecen-1-ol, 3,7,11,15-Tetramethyl-, [R-[R*,R*-(E)]]- (T-Phytol)	$C_{20}H_{40}O$	296.5	8.53
3	39.667	Undecane, 2,4-Dimethyl-	$C_{13}H_{28}$	184.36	12.25
4	40.940	But-3-en-1-yl 2-methylbutanoate	$C_9H_{16}O_2$	156.22	11.87

Fig.3 to Fig.6 show spectrums of major peaks.

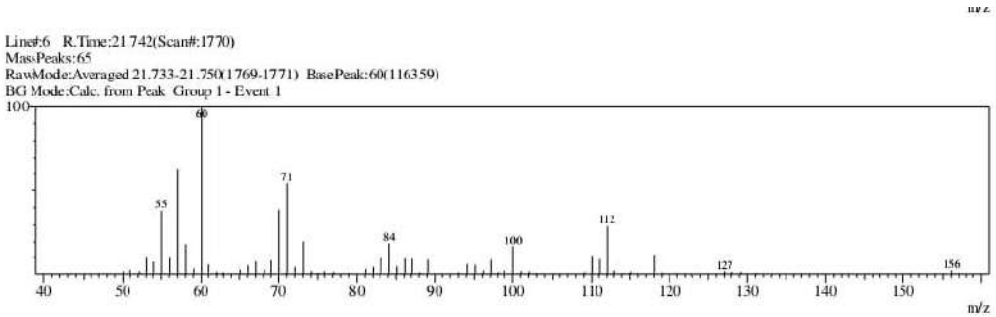


Fig.3: Spectrum of major peak at R.T. = 21.742

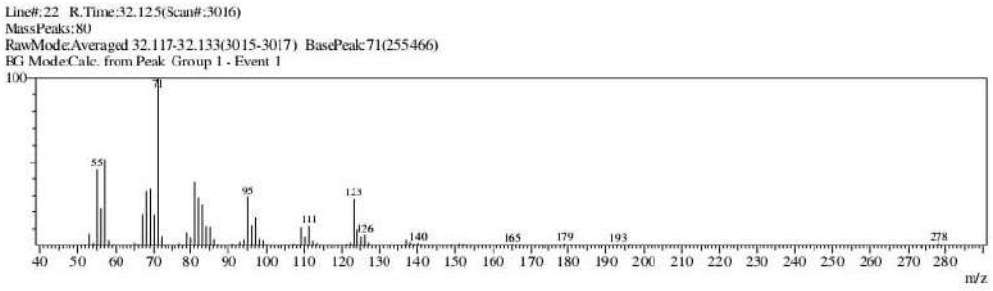


Fig.4: Spectrum of major peak at R.T. = 32.122

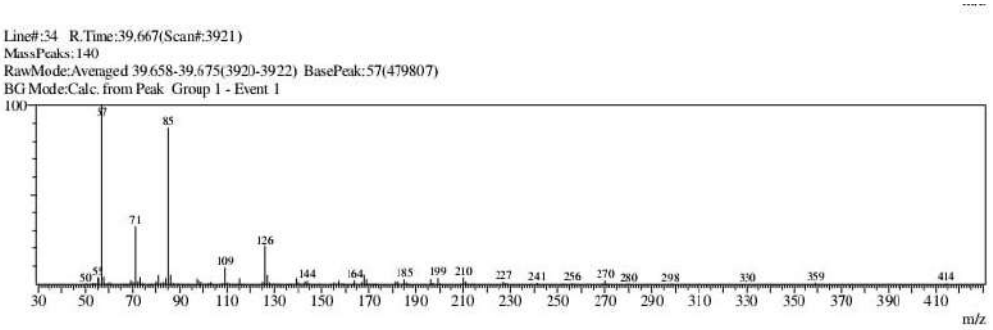


Fig.5: Spectrum of major peak at R.T. = 39.667

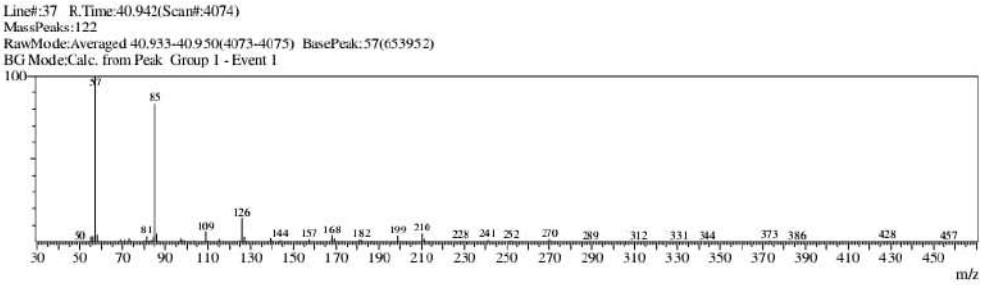


Fig.6: Spectrum of major peak at R.T. = 40.940

IV. CONCLUSION

The results are the first given information on the chemical composition of *Solanum viarum*. The methanolic leaf extract of *Solanum viarum* shows four major chemical constituents. i.e. 1,3,4,5-Tetrahydroxycyclohexanecarboxylic acid, 2-Hexadecen-1-ol, 3,7,11,15-Tetramethyl-, [R-[R*,R*-(E)]]- (T-Phytol), Undecane, 2,4-Dimethyl- and But-3-en-1-yl 2-methylbutanoate. In future, structural elucidation by NMR study and antimicrobial study will be carried out.

V. ACKWLEDGEMENT

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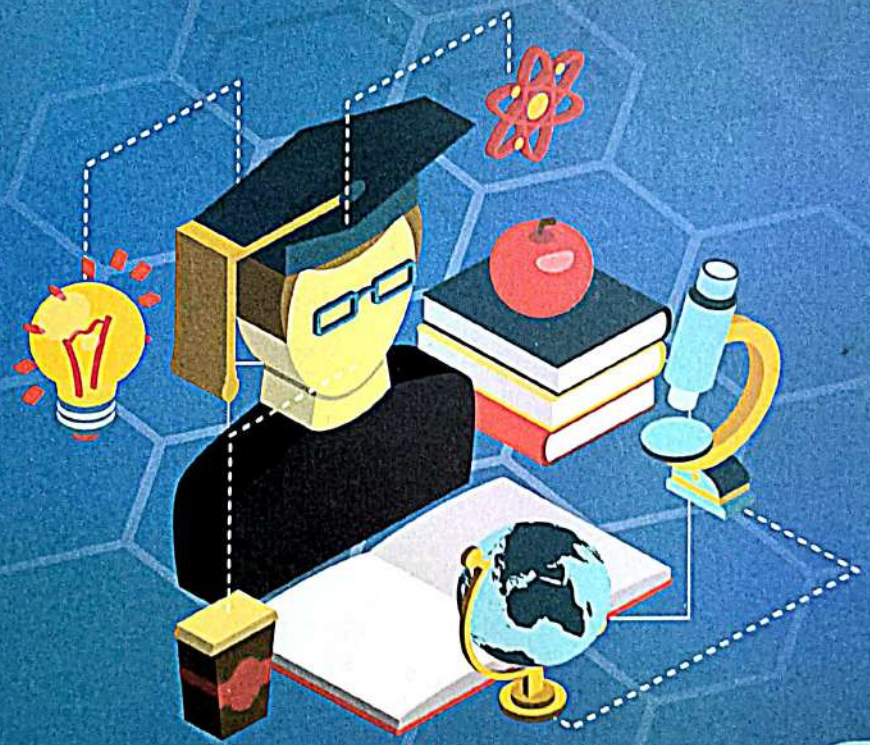
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Index

Sr. No.	Research Paper & Author	Page No.
01.	**Skill Based Education in NEP 2020: An Overview** Dr Bandu Jamnik	01-03
02.	**Challenges of NEP 2020 : Reference to the Academic & Non-academic Integration in Diverse Socio-Economic Background** Dr Rekha Kalbande	04-07
03.	**New Education Policy2020: Challenges before Studentsand Teachers** Dr Indal G. Jadhav	08-12
04.	**Electronic Commerce and Management: A Study on Challeneges in An Emerging Economy** Dr. Piyush U. Nalhe	13-19
05.	**Bridging the Linguistic Gulf: Enhancing English Language Proficiency and Engagement in Undergraduate Students from Rural and Backward Areas** Dr. Raheel K. Quraishi	20-24
06.	**Advancements in Molecular Simulation Techniquesfor Understanding Complex Systems : A Comprehensive eview** Surya Pratap Singh	25-31
07.	**National Education Policy 2020 and Online and Digital Education in the subject of Law** Prof. Hemesh Nandkishor Joshi	32-36
08.	**Human Resource Management (HRM) and Role of Teachers with respect to NEP 2020** Dr. Vasudev N. Joshi	37-41
09.	**NEP 2020 and Commerce Education** Dr.Pradip.S.Anantwar	42-45
10.	**Challenges Of National Education Policy: 2020** Dr. Suresh Namdeo Gawai	46-53
11.	**Challenges of NEP 2020-A Study** Dr. Vivek V. Patil	54-58
12.	**The Challenges and Ways of Vocationalisation of Commerce Education** Dr. Deepak Dattatray Nilawar	59-62
13.	**Skill based Education in NEP- 2020: a review** Dr.Sachin Kadu	63-68
14.	**The Evolving Role of Teachers in India's New Education Policy 2020** Dr. Vyankatesh Digambarrao More	69-71
15.	**A New Path Way in NEP 2020 : Stem Education** Dr.Rachna A.Rathi	72-76
16.	**NEP 2020 : Skill Based Education** Ku.Priti Madhukar Naphade	77-81
17.	**Impact Of Nep On The Creation of New Jobs** Miss. Priyanka Mahendrasing Pardeshi, Dr. Avinash S. Nile	82-85

18. **A Study of New Education Policy-2020 Challenges of Teachers and Students** 86-8
Dr. Saddam R. Sayyad

19. **Impact Of National Education Policy 2020** 89-9
Dr.P.N.Ladhe

20. **NEP 2020: A Tool To Make India Superpower** 93-9
Dr.Gayatri Sanjay Tiwari

21. **A Review of Principles and Issues of NEP 2020** 98-10
Dr. Anand P. Wadwale

22. **Value Education and Teacher** 103-1
Dr. Bapurao Dinaji Watode

23. **National Education Policy 2020: A Concern for Higher Education and Management Education** 108-1
Dr. Gayatri S. Chawale

24. **NEP 2020 and Higher Learning Institutions: A Comprehensive Analysis of College Involvement** 113-1
Dr. Lalchand Damodar Bodile

25. **Skill Enhancement and Teachers in Education** 118-1
Dr. Pravin P. Kulkarni

26. **A Critical Study Of NEP 2020: Issues, Approaches, Challenges, Oppertunities And Criticism** 123-1
Dr. Subhash P. Jadhao

27. **New Educaton Policy 2020 and Its Challenges** 129-1
Ms. Komal Ashok Gupta

28. **A Comparative Study of Old Education Policy and New Education Policy 2020** 133-1
Mr. Bhushan Shrirampant Mangate

29. **National Education Policy 2020: A Concern for Management Education** 138-1
Prof. Dr. Rupesh M. Kurhekar

30. **Indian Higher Education and its Challenges** 143-1
Prof. Rahul Gayakwad

31. **Environmental Attunement In Yoga, Physical Education And Sport** 148-1
Dr. Sandeep Gadadane

32. **Exploring All the Features And User Concerns Of Home Away Your Ultimate Housing Solution** 152-1
Anupam Pandey, Yash Bambal, Sakshi Bhor, Karn Datta Godse

33. **New Education Policy 2020, A Journey Toward A More Holistic and Multidisciplinary Education** 162-1
Dr. B. N. Mahajan

34. **National Education Policy 2020: A Catalyst for Skill Based Education** 166-1
Dr. Shivcharan. L. Kottewar

35. **Upcoming Challenges of New Education Policy 2020** 171-1
Dr. Vivek H. Meshram

36. **Employability of Business Education in India** 175-179
Dr. Vivek M. Morey

37. **What is National Education Policy 2020: What's the benefit of NEP to stake holders (Parent, Student, Teacher) as a Higher Education Institute?** 180-185
Prof. Ashish Rameshlal Kanhu

38. **Job Satisfaction and Impact of NEP on The Creation of New Job** 186-189
Shri. Bharat S. Deshmukh

39. **NEP 2020 and Online Education - Benefits and Challenges** 190-195
Dr. Ashish P. Mohata

40. **An Efficient Architecture For Mobile Web Services in Cloud Environment** 196-201
Dr. Dudhe Anil A., Dr. Sherekar S.S.

41. **Impact of New Education Policy 2020 on Higher Education** 202-207
Dr. Rupesh S. Mankar

42. **Comparison of National Education Policy 1986 And New Education Policy** 208-211
Dr. Sanjivani K. Parate

43. **NEP 2020: Features of NEP 2020 and Role of Teacher in NEP 2020** 212-216
Dr. Santosh P. Rathod

44. **भारतातील आरक्षण आणि राजकारण** 217-219
प्रा. डॉ. अरुण मुकुंदराव शेळके

45. **भारत की नई शिक्षा नीति – विशेषताएँ, गुण एवं दोष** 220-224
डॉ. जे. एस. सवाईथूल

46. **राष्ट्रीय शिक्षा नीति के माध्यम से भारतीय भाषाओं कला और संस्कृति का संवर्धन** 225-227
डॉ. आनंद आर. बक्षी

■ ■ ■

Impact of New Education Policy 2020 on Higher Education

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Abstract

The New Education Policy announced by Government of India (NEP 2020) was a welcoming change and fresh news amidst all the negativities surrounding the world due to the challenges posed by Covid-19 pandemic. The announcement of NEP 2020 was purely unexpected by many. The changes that NEP 2020 has recommended were something that many educationists never saw coming. Though the education policy has impacted school and college education equally, this article mainly focuses on NEP 2020 and its impact on Higher Education. This paper also outlines the salient features of NEP and analyses how they affect the existing education system.

Introduction :

The National Education Policy 2020 (NEP 2020), launched on 29 July 2020, outlines the vision of India's new education system. NEP 2020 focuses on five pillars: Affordability, Accessibility, Quality, Equity, and Accountability – to ensure continual learning. It has been crafted consistent with the needs of the citizens as a demand for knowledge in society and economy called for a need to acquire new skills on a regular basis. Thus, providing quality education and creating lifelong learning opportunities for all, leading to full and productive employment and decent work as enlisted in United Nations Sustainable Development Goals 2030, forms the thrust of NEP 2020. The new policy replaces the previous National Policy on Education, 1986 and forms a comprehensive framework to transform both elementary and higher education in India by 2040. The NEP 2020 calls for key reforms in both school and higher education that prepare the next generation to thrive and compete in the new digital age. Thus, there is much emphasis upon multidisciplinary, digital literacy, written communication, problem-solving, logical reasoning, and vocational exposure in the document.

The NEP 2020 was conceived to raise the Gross Enrolment Ratio (GER) from the current 26 percent to 50 percent by 2030 in the higher education space. It aims at building the overall personality of students by strengthening infrastructure for open and distance learning, online education and increasing the use of technology in education. Moreover, the National Research Foundation (NRF) will be set up to boost research work in the country. A National Accreditation Council (NAC) envisaged as a single regulator for higher education institutions across the country will be established. The Higher Education Council of India (HECI) will have multiple verticals to fulfill various roles. Efforts will be undertaken to set up a National Recruitment Agency for all government recruitment exams, and a Common Eligibility Test (CET) for various recruitment exams of the same level.

Moreover, the courses and programs in subjects, such as Indology, Indian languages, AYUSH systems of medicine, yoga, arts, music, history, culture, and modern India, internationally relevant curricula in the sciences, social sciences, and beyond, meaningful opportunities for social

engagement, quality residential facilities and on-campus support, etc. will be fostered to attain this goal of global quality standards.

Objectives of the study:

The primary objective of this research is to study the impact of New Education Policy 2020 on higher education. The study also outlines the salient features of NEP 2020 and analyses how they affect the existing education system in India.

Research methodology:

This research is a descriptive study. The necessary secondary data was collected from various websites including those of Government of India, journals, other publications, magazines, etc. This data was then analyzed and reviewed to arrive at the conclusions.

SALIENT FEATURES OF NEP RELATED TO HIGHER EDUCATION:

National Education Policy 2020 has been announced on 29 July 2020. The National Education Policy 2020 proposes various reforms in school education as well as higher education including technical education. A number of action points/activities for implementation in school education as well as higher education are mentioned in the National Education Policy.

Details of the salient features of NEP 2020 are as follows-

1. Ensuring Universal Access at All Levels of schooling from pre-primary school to Grade 12;
2. Ensuring quality early childhood care and education for all children between 3-6 years;
3. New Curricular and Pedagogical Structure (5+3+3+4);
4. No hard separations between arts and sciences, between curricular and extra- curricular activities, between vocational and academic streams;
5. Establishing National Mission on Foundational Literacy and Numeracy;
6. Emphasis on promoting multilingualism and Indian languages; The medium of instruction until at least Grade 5, but preferably till Grade 8 and beyond, will be the home language/mother tongue/local language/regional language.
7. Assessment reforms - Board Exams on up to two occasions during any given school year one main examination and one for improvement, if desired;
8. Setting up of a new National Assessment Centre, PARAKH (Performance Assessment Review, and Analysis of Knowledge for Holistic Development);
9. Equitable and inclusive education - Special emphasis given on Socially and Economically Disadvantaged Groups (SEDGs);
10. A separate Gender Inclusion fund and Special Education Zones for disadvantaged regions and groups;
11. Robust and transparent processes for recruitment of teachers and merit based performance;
12. Ensuring availability of all resources through school complexes and clusters;
13. Setting up of State School Standards Authority (SSSA);
14. Exposure of vocational education in school and higher education system;
15. Increasing GER in higher education to 50%;

16. Holistic and Multidisciplinary Education with multiple entry/exit options;
17. NTA to offer Common Entrance Exam for Admission to HEIs;
18. Establishment of Academic Bank of Credit;
19. Setting up of Multidisciplinary Education and Research Universities (MERUs);
20. Setting up of National Research Foundation (NRF);
21. Light but Tight' regulation;

NEP, 2020 aim to increase the GER to 100% in preschool to secondary level by 2030 whereas GER in Higher Education including vocational education from 26.3% (2018) to 50% by 2035.

The Central Sector Scheme **Pandit Madan Mohan Malaviya National Mission on Teachers and Teaching (PMMMNMTT)** was launched in 2014 to address comprehensively all issues related to Teacher Training/ Capacity Building and Professional Development of Teachers. Under the components, the total 95 centers were established throughout the country through which faculties/Teachers have been trained. Currently, The Standing Finance Committee has appraised the Scheme and recommended for continuation till 2025-2026 with the total outlay of Rs. 493.68 corer. Under the PMMMNMTT Scheme centers are established on the basis of the proposals received from education institutions, their screening by Screening Committee and approval by Project Approval Board.

Issues of NEP 2020

- Early streaming of students into different disciplines.
- Lack of access to HE, especially in socio-economically disadvantaged areas which resulted in the current gross enrolment ratio (GER) of 25% only.
- Lack of teacher and institutional autonomy to make innovations in HE to attract many students.
- Insufficient mechanisms for career management and progression of faculty and institutional leaders.
- The lack of research and innovations at most of the universities and colleges.
- Suboptimal levels of governance and leadership at higher education institutions.
- A corrupted regulatory system allowing fake colleges to thrive while constraining excellent, innovative institutions.

Expansion of open and distance learning to increase Gross Enrolment Ratio (GER)

Internationalization of Education Professional Education will be an integral part of the higher education system. Stand-alone technical universities, health science universities, legal and agricultural universities, or institutions in these or other fields, will aim to become multi-disciplinary institutions. Teacher Education - 4-year integrated stage-specific, subject- specific Bachelor of Education Establishing a National Mission for Mentoring.

Creation of an autonomous body, the National Educational Technology Forum (NETF) to provide a platform for the free exchange of ideas on the use of technology to enhance learning, assessment, planning, administration. Appropriate integration of technology in to all levels of education.

a. Achieving 100% youth and adult literacy.

b. Multiple mechanisms with checks and balances will combat and stop the commercialization of higher education.

c. All education institutions will be held to similar standards of audit and disclosure as a 'not for profit' entity.

d. The Centre and the States will work together to increase the public investment in Education sector to reach 6% of GDP at the earliest.

e. Strengthening of the Central Advisory Board of Education to ensure coordination to bring overall focus on quality education.

NEP, 2020 aim to increase the GER to 100% in preschool to secondary level by 2030 whereas GER in Higher Education including vocational education from 26.3% (2018) to 50% by 2035.

DETAILED ANALYSIS OF IMPACT OF NEP ON HIGHER EDUCATION

Regulatory System of Higher Education:

A significant change in NEP 2020 is the proposal to set up the Higher Education Commission of India (HECI), as an umbrella body for higher education, excluding medical and legal education. This will usually bring out a question that what will happen to the present UGC and AICTE? HECI is aiming at reforming the higher education sector; the Bill will separate the Academic and Funding aspects of the sector. According to the new Bill, HECI will not have any financial powers. The funding processes which were handled by the University Grants Commission (UGC) will be taken care by the Ministry of Education, previously known as the Ministry of Human Resource Development (MHRD). This change however is expected to clear the regulatory mess in India's Higher Education system. HECI is expected to have four independent verticals - National Higher Education Regulatory Council (NHERC) for regulation, General Education Council (GEC) for standard-setting, Higher Education Grants Council (HEGC) for funding, and National Accreditation Council (NAC) for accreditation. To have uniformity in education standards, a single umbrella body was always a requirement and this has been a vision of numerous educationists. This is considered as the right step in streamlining education policy. However, to ensure quality of higher education, institutes must be measured based on relevant parameters like research, industry linkages, placements and academic excellence, etc. If the HECI can manage this, the benefits to its biggest stakeholder, the youth of India, might be significant.

Opportunities of NEP 2020

New education Policy begins with the unfinished agenda of NEP — 1986. NEP — 1986 was rooted in a very different India. Over the years, remarkable strides have been made in terms of access and equity. Near universal levels of enrolment at primary levels, and subsequent increase in enrolment at higher education levels (GER: 26.3%) have been achieved. However, there has also been a drop in the quality of learning in public school systems, followed by an exodus of elite and middle classes. This also led to the weakening of accountability mechanisms. Despite poor returns on learning, the pay-structures in public systems have seen a gradual increase.

Graded Accreditation and Graded Autonomy:

The concept of "empowerment and autonomy to innovate" is one of the key features in NEP 2020 which supports a "phasing out" strategy from Affiliated Colleges to Autonomous Institutions. The increased flexibility offered to autonomous institutions also gives hope in curriculum enrichment. It also says that with appropriate accreditations, Autonomous degree-

granting Colleges could evolve into Research-intensive or Teaching-intensive Universities, if they so aspire. The announcement of setting up Multidisciplinary Education and Research Universities (MERUs) in the country gives more hope. These institutions will be at par with the existing IITs and IIMs and will aim to showcase multidisciplinary education for the Indian students. Another important change the NEP 2020 suggests that the National Testing Agency will serve as a premier, expert, autonomous testing organization to conduct entrance examinations for undergraduate and graduate admissions and fellowships in Higher Education Institutions. The high quality, range, and flexibility of the NTA testing services will enable most universities to use these common entrance exams - rather than having hundreds of universities each devising their own entrance exams - thereby drastically reducing the burden on students, universities and colleges, and the entire education system. It will be left up to individual universities and colleges to use NTA assessments for their admissions. It also surely helps the students to easily transfer their degrees and credits to universities abroad.

More Holistic and Multidisciplinary Education:

The NEP 2020 claims that, a holistic and multidisciplinary education would aim to develop all capacities of human beings -intellectual, aesthetic, social, physical, emotional, and moral in an integrated manner. Such an education will help develop well-rounded individuals that possess critical 21st century capacities in fields across the arts, humanities, languages, sciences, social sciences, and professional, technical, and vocational fields; an ethic of social engagement; soft skills, such as communication, discussion and debate; and rigorous specialization in a chosen field or fields. The NEP 2020 envisions one large multidisciplinary Higher Education Institution (HEI) in or near every district, by 2030.

The structure and lengths of degree programmers:

In the context of the National Education Policy 2020 scheme, any undergraduate degree in any institution will be of duration of three or four years. One can leave the degree within this period. Any educational institution will have to give to the student a diploma degree after the student completes two years of study, a degree after the student completes three years of study and a certificate to those students who complete one year of study in any professional or vocational course of their choice. The Government of India will also help in establishing an Academic Bank of Credit for storing the academic scores digitally. This will enable the institutions to count the credit at the end and put it in the degree of the student. This will be helpful for those individuals who might have to leave the course mid-way. They can start the course later on from where they left off and not start from the beginning once again. Even though NEP 2020 says that Higher education institutions will be given the freedom to start PG courses there may be some difficulty in designing One Year PG Degree for students who have completed 4 Year UG Degree and a Two Year PG Degree for students who have completed 3 Year UG Degree.

CONCLUSION :

The new national education policy 2020 is a good policy as it aims at making the education system holistic flexible multi-disciplinary align to the needs of 21st century and the 2030 sustainable development goals. The new national education policy 2020 is a good policy as it aims at making the education system holistic flexible, multi-disciplinary align to the needs of 21st century and the 2030 sustainable development goals. NEP, 2020 aim to increase the GER to 100% in preschool to secondary level by 2030 whereas GER in Higher Education including vocational education from 26.3% (2018) to 50% by 2035. With an aim to create a more inclusive cohesive and productive nation the recently unveiled national education policy 2020 has come a groundbreaking reform by the Ministry of human resource development MHRD.

The intent of policy seems to be ideal in many ways but it is the implementation where lies the key to success. Under the NEP 2020, the focus areas of the reforms seek to cultivate 21st century skills among students including critical thinking problem solving creativity and digital literacy. As technological advancements rapid globalisation and unprecedented developments such as the covid-19 pandemic – transform the future of work, the existing education models need to be reassessed in keeping with the challenges of the global economy duct of an extensive exercise that strives to achieve 100% gross enrollment ratio by 2030. With an aim to create a more inclusive cohesive and productive nation the recently unveiled NEP2020 has come a groundbreaking reform by the Ministry of human resource development MHRD. The intent of policy seems to be ideal in many ways but it is the implementation where lies the key to success. Under the NEP 2020, the focus areas of the reforms seek to cultivate 21st century skills among students including critical thinking, problem solving creativity and digital literacy.

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Index

Sr. No.	Research Paper & Author	Page No.
01.	**Skill Based Education in NEP 2020: An Overview** Dr Bandu Jamnik	01-03
02.	**Challenges of NEP 2020 : Reference to the Academic & Non-academic Integration in Diverse Socio-Economic Background** Dr Rekha Kalbande	04-07
03.	**New Education Policy2020: Challenges before Studentsand Teachers** Dr Indal G. Jadhav	08-12
04.	**Electronic Commerce and Management: A Study on Challeneges in An Emerging Economy** Dr. Piyush U. Nalhe	13-19
05.	**Bridging the Linguistic Gulf: Enhancing English Language Proficiency and Engagement in Undergraduate Students from Rural and Backward Areas** Dr. Raheel K. Quraishi	20-24
06.	**Advancements in Molecular Simulation Techniquesfor Understanding Complex Systems : A Comprehensive eview** Surya Pratap Singh	25-31
07.	**National Education Policy 2020 and Online and Digital Education in the subject of Law** Prof. Hemesh Nandkishor Joshi	32-36
08.	**Human Resource Management (HRM) and Role of Teachers with respect to NEP 2020** Dr. Vasudev N. Joshi	37-41
09.	**NEP 2020 and Commerce Education** Dr.Pradip.S.Anantwar	42-45
10.	**Challenges Of National Education Policy: 2020** Dr. Suresh Namdeo Gawai	46-53
11.	**Challenges of NEP 2020-A Study** Dr. Vivek V. Patil	54-58
12.	**The Challenges and Ways of Vocationalisation of Commerce Education** Dr. Deepak Dattatray Nilawar	59-62
13.	**Skill based Education in NEP- 2020: a review** Dr.Sachin Kadu	63-68
14.	**The Evolving Role of Teachers in India's New Education Policy 2020** Dr. Vyankatesh Digambarrao More	69-71
15.	**A New Path Way in NEP 2020 : Stem Education** Dr.Rachna A.Rathi	72-76
16.	**NEP 2020 : Skill Based Education** Ku.Priti Madhukar Naphade	77-81
17.	**Impact Of Nep On The Creation of New Jobs** Miss. Priyanka Mahendrasing Pardeshi, Dr. Avinash S. Nile	82-85

Scanned with CamScanner

18. **A Study of New Education Policy-2020 Challenges of Teachers and Students** 86-88
Dr. Saddam R. Sayyad

19. **Impact Of National Education Policy 2020** 89-92
Dr.P.N.Ladhe

20. **NEP 2020: A Tool To Make India Superpower** 93-97
Dr.Gayatri Sanjay Tiwari

21. **A Review of Principles and Issues of NEP 2020** 98-102
Dr. Anand P. Wadwale

22. **Value Education and Teacher** 103-107
Dr. Bapurao Dinaji Watode

23. **National Education Policy 2020: A Concern for Higher Education and Management Education** 108-112
Dr. Gayatri S. Chawale

24. **NEP 2020 and Higher Learning Institutions: A Comprehensive Analysis of College Involvement** 113-117
Dr. Lalchand Damodar Bodile

25. **Skill Enhancement and Teachers in Education** 118-122
Dr. Pravin P. Kulkarni

26. **A Critical Study Of NEP 2020: Issues, Approaches, Challenges, Oppertunities And Criticism** 123-128
Dr. Subhash P. Jadhao

27. **New Educaton Policy 2020 and Its Challenges** 129-132
Ms. Komal Ashok Gupta

28. **A Comparative Study of Old Education Policy and New Education Policy 2020** 133-137
Mr. Bhushan Shrirampant Mangate

29. **National Education Policy 2020: A Concern for Management Education** 138-142
Prof. Dr. Rupesh M. Kurhekar

30. **Indian Higher Education and its Challenges** 143-147
Prof. Rahul Gayakwad

31. **Environmental Attunement In Yoga, Physical Education And Sport** 148-151
Dr. Sandeep Gadadane

32. **Exploring All the Features And User Concerns Of Home Away Your Ultimate Housing Solution** 152-161
Anupam Pandey, Yash Bambal, Sakshi Bhor, Karn Datta Godse

33. **New Education Policy 2020, A Journey Toward A More Holistic and Multidisciplinary Education** 162-165
Dr. B. N. Mahajan

34. **National Education Policy 2020: A Catalyst for Skill Based Education** 166-170
Dr. Shivcharan. L. Kottewar

35. **Upcoming Challenges of New Education Policy 2020** 171-174
Dr. Vivek H. Meshram

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National Education Policy 2020: A Catalyst for Skill Based Education

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Abstract:

Skill development helps to increase the productivity and employability of workforce both in the organized and the unorganized sectors. Skill gap is affecting the employability scenario in almost every sector. However, the National Education Policy 2020 is perceived to be a blessing in disguise in such a scenario that will help bridge this gap by providing students with industry-relevant skills so as to make them future-ready professionals. This research paper is trying to discuss the Government efforts for skill development and status of skill gap in India. It further studied the catalytic role of NEP in skill development.

Keywords: National Education Policy, Vocational Training, Skill Development etc.

Introduction:

Skills and knowledge are the driving forces of economic growth and social development for any country. Countries with higher levels and better standards of skills adjust more effectively to the challenges and opportunities in domestic and international job markets. India currently faces a severe shortage of well-trained, skilled workers. It is estimated that only 2.3 % of the workforce in India has undergone formal skill training as compared to 68% in the UK, 75% in Germany, 52% in USA, 80% in Japan and 96% in South Korea. Large sections of the educated workforce have little or no job skills, making them largely unemployable. Therefore, India must focus on scaling up skill training efforts to meet the demands of employers and drive economic growth.

Statement of the Problem:

India is one of the youngest nations in the world, with more than 54% of the total population below 25 years of age and over 62% of the population in the working age group (15-59 years). This demographic advantage is predicted to last only until 2040. India therefore has a very narrow time frame to harness its demographic dividend and to overcome its skill shortages. India's skilling challenge is further affected by the fact that skill training efforts cut across multiple sectors and require the involvement of diverse stakeholders such as: multiple government departments at the centre and state levels, private training providers, educational and training institutions, employers, industry associations, assessment and certification bodies and trainees. All these stakeholders need to align their work together in order to achieve the target of 'Skill India'.

Objectives of the Study:

Following are the objectives of this study:

1) To study the institutional initiatives for skill enhancement and development.

2) To analyse the status of skill gap in India and to understand the benefits of skill development.

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3) To study the catalytic role of NEP 2020 in skill development.

Research Methodology:

To study the role of NEP 2020 in skill development in India researcher studied and analysed theoretical and literature reviews. This study is based on secondary data and trying to add to the existing literature on NEP 2020 and skill development.

Government Efforts for Skill Enhancement and Development:

The institutional initiatives taken by the government skill enhancement and development are as follows:

1) The Ministry of Skill Development and Entrepreneurship was set up in November 2014 to drive the 'Skill India' agenda in a 'Mission Mode' in order to converge existing skill training initiatives and combine scale and quality of skilling efforts, with speed.

2) The Ministry also launched the National Mission for Skill Development to provide the overall institutional framework to rapidly implement and scale up skill development efforts across India.

3) The Mission consists of a Governing Council at apex level, a Steering Committee and a Mission Directorate as the executive arm of the Mission.

4) Mission Directorate is supported by three other institutions: National Skill Development Agency (NSDA), National Skill Development Corporation (NSDC), and Directorate General of Training (DGT) – all of which have linkages with Mission Directorate to facilitate smooth functioning of the national institutional mechanism.

5) At State level, states are also encouraged to create State Skill Development Missions (SSDM) along the lines of National Skill Development Mission with a Steering Committee and Mission Directorate at State level.

Status of Skill Gap in India:

Unemployment is not a new issue in our country. According to India Skills Report 2022 by Wheebox, only 48.7% of total youth in India is employable. This means almost 1 out 2 Indian youths are not employable. The study also says that about 75% of all the companies surveyed reported a skill gap in the industry. Skill gap is affecting the employability scenario in almost every sector. As per the International Labor Organization, there will be a skill deficit of 29 million by 2030, which will significantly affect the country's GDP. According to a research conducted by NASSCOM, every year more than 3 million graduates and post-graduates are added to the Indian human-resource and out of these, only 25% of IT graduates are considered employable by fast growing IT & ITES industry.[2] According to a survey by Skillsoft, the skills gap in the information technology sector is getting significantly worse, as the industry grapples with talent shortage and employee retention. A whopping 66% of IT decision-makers see skill gaps in their teams as a major problem. The study found that the skill gap problem is being driven by both difficulties in hiring and retaining workers as well as underinvestment in training and development opportunities for existing staff.[3]

Benefits of Skill Development:

The benefits of Skill Development are:

1) Skill development helps to create a workforce empowered with the necessary and continuously upgraded skills, knowledge and internationally recognized qualifications to gain access to decent employment and ensure India's competitiveness in the dynamic global market.

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2) It helps to increase the productivity and employability of workforce both in the organized and the unorganized sectors.

3) It also helps to increase participation of youth, women, disabled and other disadvantaged sections of the society.

4) It synergizes efforts of the various sectors.

5) It assists to fulfil labour market demands.

Catalytic Role of NEP in Skill Development:

The introduction of the National Educational Policy 2020 is considered as a bold and revolutionary move for the Indian education industry. It is expected to improve the educational standards for students both in schools as well as in colleges. The proposal to introduce vocational education from sixth grade onwards and create a National Committee for the Integration of Vocational Education (NCIVE) is viewed as a reform that will certainly take the Indian educational market to the zenith in the times to come.[5] The policy will play a vital role in equipping the manpower of the country to bring about a change, especially in educational practices, along with putting an emphasis on developing technical as well as soft skills amongst graduate and post-graduate students. NEP 2020 focuses on employability and acknowledges the role of education in providing students with the right skillsets. The vision of the government via this initiative is to meet the 2030 Agenda for Sustainable Development, which strives to ensure inclusive and equitable education as well as promote lifelong learning opportunities for all.[6]

Due to the skill gap, businesses are unable to find and recruit talent that matches their expectations due to the lack of futuristic skills. The major reason for this is the inadequacies in our education system along with the companies not prioritizing on-job training. However, the National Education Policy 2020 is perceived to be a blessing in disguise in such a scenario that will help bridge this gap by providing students with industry-relevant skills so as to make them future-ready professionals.[7] The National Education Policy 2020 promotes a creative and multidisciplinary curriculum that has broken the shackles of subject choices being limited to the traditional domains of Science, Commerce and Humanities. It allows for cross sectional course selection and gives students the opportunity to enhance their core skills.

NEP also recognizes the importance of soft skills such as communication, team work, problem solving, decision making, analytical thinking, resiliency, etc. as imperative life skills. Along with academic knowledge, leadership skills are also inculcated amongst the students so that they can benefit ahead in their career trajectory. NEP allows foreign universities to set up their campuses and operate in India. This will help students have access to global quality education along with international exposure. They will be prepared for facing competition and be prepared to be at par with global standards. This will help them focus on shaping themselves as per the chosen career path right from the beginning.

Need for Skill Base Education

In India, around 250 million students were affected due to school closures at the onset of lockdown induced by COVID-19. COVID-19 has brought about a drastic change in the education system not only in India but also in the entire world. In the wake of the Covid-19 pandemic situation and the imposed lockdown, online classes were conducted at the college and university level. Today, digital learning has emerged as a necessary resource for students and schools all over the world. For many educational institutes, this is an entirely new way of education that they have had to adopt. Online learning is now applicable not just to learn academics but it also extends to learning

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extracurricular activities for students as well. COVID-19 pandemic has highlighted the importance of online education as a modern method of learning.

Benefits of online education

1) **Accessibility of Time And Place:** Online education is allows students to attend classes from any location of their choice. It also allows schools to reach out to a more extensive network of students, instead of being restricted by geographical boundaries. Additionally, online lectures can be recorded, archived, and shared for future reference. This allows students to access the learning material at a time of their comfort.

2) **Reduces migration**: Many students move to urban areas for quality education. Online education has restricted migration as it has made education accessible to the rural hinterlands. Now student can learn and get a degree while sitting at the comfort of their home. It's possible to connect with teachers and learners all around the world with online courses.

3) **Low cost: Online education is more affordable as compared to old fashioned education. Additional expenses like uniform cost, travel expenses in the old education system are not required to be incurred in this modern education system.** Additionally, all the course or study materials are available online, thus creating a paperless learning environment which is more affordable, while also being beneficial to the environment. **Financially weaker students can fulfill their dreams due to this advantage of online education.**

4) **Efficiency:** Online learning offers teachers an efficient way to deliver lessons to students. Online learning has a number of tools such as videos, PDFs, podcasts, and teachers can use all these tools as part of their lesson plans. By extending the lesson plan beyond traditional textbooks to include online resources, teachers are able to become more efficient educators.

5) **Tech savvy: As students use technology to learn, they can become tech-savvy through digital learning. In today's technological age, most of the jobs require tech-savvy employees.**

6) **Less competition & less intensity:** As you see there can be less intense and less competition in online learning compared to traditional classes. You have to memorize that the low level of competition makes students less stressed and more relaxed.

7) **Improves time management:** A student has to learn how to manage their time efficiently. Digital classes make this possible as there are no teachers to guide the students physically in doing their work. This independence allows students to grow and improve their time management abilities.

Concluding Remark:

With the advent of Industry 4.0, many trends are gaining prominence, and NEP 2020 is no exception. Restructuring the educational ecosystem is a critical first step in dealing with the rapid changes occurring in response to demands and needs. In a nutshell, the strong skill-based education model has the potential to not only change the way the country views career opportunities, but also to take a creative and innovative approach to global leadership.

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- **शके १९४५**
- **वर्ष : ९२**
- **पुरवणी अंक : ४७**

संपादक मंडळ

- प्राचार्य डॉ. सर्जेराव भामरे
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✷ प्रकाशक ✷

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अनुक्रमणिका

१. **A Bibliometric Study of Research Output On Green Computing**

- Mrs. Jyotsna S. Moon ---------- ९

२. **Digital Library in Modern Era: Services, Challenges and Opportunities**

- Asst. Prof. Kumarswami Nanaji Durge ---------- १४

३. **Applications And Advancement in Cloud Computing : Innovations Ennovations Enhancing The Library Services**

- Assistant Prof. Sachin G. Karnewar ---------- १८

४. **Awareness and Use of Social Media Platforms by Librarians working in Academic Colleges of Chandrapur and Gadchiroli District**

- Dr. Pravin B. Gohane ---------- २३

५. **Semantic Web and the Digital Libraries: An analysis**

- Mr. Dilip P. Sontakke ---------- २८

६. **Cloud Computing execution for effective library services**

- i) Dr Kishor N. Wasurke, ii) Dr. Anil M. Chahande ---------- ३२

७. **Digital Horizons : Exploring Technology-Driven Library Services**

- Mr. Sandeep A. Meshram ---------- ३७

८. **Use of Digital Library Lirvices And Its Applications in The Information Age**

- Dr. Prashant S. Pagade ---------- ४२

९. **Emerging Innovations in Learnings : Technological Compatibility Among The Professionals of The Libraries**

- Mr. Mangesh Shamrao Karambe ---------- ४६

ISSN No. 2394-5990

४७. **लघु उद्योगांच्या विकासात निर्माण होणाऱ्या समस्या**
- Imran Usman Sheikh ---------- २३१

४८. **पारंपारिक विपणन व डिजीटल विपणनाचे चंद्रपूर जिल्ह्यातील ग्राहकांवर होणाऱ्या परिणामांचे तुलनात्मक अध्ययन : विशेष संदर्भ उपभोग्य वस्तू**
- १) अनिकेत हरेश गजभिये, २) प्रा. डॉ. रेखा बी. मेश्राम ---------- २३५

४९. **चंद्रपूर जिल्ह्यांतर्गत हंगामी रोजगारासाठी स्थलांतरण करणाऱ्या शेतमजुरांच्या आर्थिक स्थितीचे अध्ययन**
- १) प्रफुल नारायण घोडाम, २) डॉ. फुलचंद निरंजने ---------- २४१

५०. **प्रधानमंत्री पिक विमा योजना आणि शेतक–याचा सहभाग**
- १) दिलीप भिमराव मेंढे, २) डॉ. विजय वि. टोंगे ---------- २४३

५१. **गडचिरोली जिल्हयाच्या आर्थिक विकासात बांबू उत्पादनाची भूमीका**
- डॉ. मोरेश्वर जिवतुराम मेश्राम ---------- २४७

५२. **Economic and Social Problems of Adivasis at Melghat and Constructive Measures**
- Dr. Praful S.Vairale ---------- २५१

५३. **Contribution of Dairy Co-Operative Society in Socio-Economic Development of Chikhaldara Taluka**
- Dr. Shivcharan. L. Kottewar ---------- २५३

५४. **A Comparative Study of Sources of Stress in Physical Education lecturers of Rural and Urban Area of East Vidarbha**
- Dr. Rahul Madhukarrao Rode ---------- २५७

५५. **Career Opportunites in Sports And Physical Education**
- Dr. Murlidhar W. Rukhmode ---------- २६२

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CONTRIBUTION OF DAIRY CO-OPERATIVE SOCIETY IN SOCIO-ECONOMIC DEVELOPMENT OF CHIKHALDARA TALUKA

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Introduction:

In comparison to other locations, the Amravati Region has extremely little rainfall on average—between 25 and 40 inches. Toor, groundnuts, cotton, and jawar are the principal crops grown in the area. Because there is a shortage of water and food during the summer, animals migrate. The Amravati district's Chikhaldara and Dharni Tahasils are completely encircled by hills and forests. These Tahasils' inner isolation and dearth of road infrastructure contribute to the neglect of several communities.

Melghat is located at the northernmost point of Maharashtra's Amravati district, near the Madhya Pradesh border, in the southwest Satpura mountain ranges. "Meeting of the Ghats" is what Melghat signifies. In 1974, the Melghat region was designated as a Tiger reserve. Their primary occupations are agriculture and the gathering of forest products. The population is primarily tribal, consisting primarily of the Korku Tribe and other tribes like Gond, Gawali, Gaolan, etc. Their primary source of income is the breeding and milking of cattle. Nonetheless, their home-based, unorganized company is flourishing. As a result, they have several challenges in effectively managing the milking business. The major issues in their lives include migration, famine, malnutrition, unemployment, poverty, and illiteracy. Maharashtra and India are seeing a sharp increase in the number of milk cooperative societies. The lives of rural milkmen have transformed as a result of cooperative milk cooperatives. Nevertheless, the cooperative movement does not extend to Melghat's impoverished areas. It is anticipated that the emergence of milk co-ops will bring about radical transformations in the lives of milkmen in the Melghat region. In order to address the aforementioned issues and promote the social and economic advancement of the people in the Melghat region, the creation of cooperative milk societies will offer new opportunities in the areas of employment, education, health, and welfare.

The cooperative movement's function in the dairy industry :

The development and economy both benefit greatly from cooperative dairying. Cooperative refers to the act of working as a team to achieve specific goals. Rural areas are where cooperative societies are primarily developed. Cooperative societies exist at the local, regional, and national levels in the modern era. Without examining the function of milk cooperative societies, research on the dairy industry cannot be considered complete. Dairy activities are developed cooperatively in Maharashtra thanks to the state government's strong interest and farmers' support. These days, a three tire system forms the basis of the dairy industry.

The structure of co-operative dairy is as follows :

I) The Maharashtra state co-operative Milk Federation Ltd.at the top level
II) District of Taluka co-operative Milk Federation at District level.
III) Primary co-operative Milk producing societies at village level.

The dairy cooperative is established with a basic objective to provide income generating activity to the small and marginal farmers and agriculture labours.

(iii) Origin of Research Problem :

Melghat is a remote and hilly area in Amravati District it comprises Chikhaldara and Dharni Tehsils. It is predominantly a tribal area resided by Korku, Gond and Gawali etc. their main occupation is farming and milking. Milk business is their domestic business and is in unorganised sector. They have less number of milk producing animals. They have to face many economic problems such as lack of capital, less milk production; storage and distribution problems, health and fodder of livestock etc. and therefore they have to live life below poverty level. Development of co-operative dairy business will result in favourable changes in their economic condition and standard of living. The main objective of the research project is to study the economic problems of milkmen in Melghat area and to find remedies to overcome their problems and bring economic development of the people living in the region.

Aims and Objective :

- To study the livelihood of Tribal person living in Chikhaldara Taluka.
- To study the lively hood of milkmen living in Chikhaldara Taluka.
- To study the socio economic problems of Milkmen.
- To study the problems of milk business in unorganised sector.
- To study the opportunity of employment generation through co-operation of milk societies.
- To study the role of co-operative milk societies in overcoming the problems of milkmen in Chikhaldara Taluka.

Hypothesis :

The establishment of cooperative milk societies will help milkmen address their social and economic problems and will boost Chikhaldara Taluka's economy.

Research Methodology:

All of the information used in this study was gathered from secondary sources, including government publications, NDDB annual reports, economic surveys, and publications from websites that address different facets of the dairy industry. In the Melghat region, there are two Tehasil Chikhaldara and Dharni, which consist of 171 and 159 villages, respectively. Thirty villages were chosen from Chikhaldara Tehsil for primary data collection via Google Form. For the purpose of the study, five household milkmen (30 x 5) = 150 household milkmen, were chosen from each village. With the aid of interviews, questionnaires, and schedules, a direct investigation into the problems and way of life of milkmen was carried out.

Need of co-operative movement in Chikhaldara Taluka:

Less milk was produced in the area as a result of factors such as unpredictable rainfall, a lack of cross-bred animals and green fodder, poor farmer response to cross-breeding, and poor farmer financial standing. Since almost all of the animals in the area are of native breeds, most farmers utilize them for purposes other than milk production in the home. In the Amravati region, "dairying" is viewed as a side business; no one treats it as their primary business. Conversely, a large number of farmers in Marathwada and Western Maharashtra consider "dairying" to be their primary business, as evidenced by the region's and Pune's milk procurement statistics. Additionally, there is a reduction in the area under irrigation, so it is imperative to increase the same

An essential part of Chikhaldara Taluka's development is the dairy cooperatives. It helps lower poverty in rural areas and provides job opportunities for jobless people. The growth of the dairy industry is crucial to the Trible people's development. Dairy societies were established with the noble goal of

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assisting their members in developing their economies. The expansion and advancement of the dairy cooperative in Chikhaldara and Melghat region is the main topic of this research. Through cooperative societies, the Dairy Development Department collects and purchases milk from milk producers. The Work that collect milk from societies, deliver it to milk chilling facilities, and finally take it to the district level for pasteurization or product manufacturing are managed by the Milk Cooperative Society. 5000 litres/day capacity milk chilling centre was established in the year 1992 at Semadoh, the tribal area of Melghat Forest. The centre mainly functions in the flush season of milk i.e. from July to December every year. The maximum average per day milk collection in the area is 200 litres. Due to scarcity of fodder and water, maximum milk producers migrate to other areas and hence the chilling centre remain closed for about 6 months every year. This area comes under Dense Forest area. Moreover, poor road facilities particularly in rainy season affect milk production. If sufficient water and all weather road facilities are made available, it will help to increase the financial and social condition of the Adivasies in this area.

			Milk Collected Yearly	
Taluka	Number Of CO-Operative Dairy Societies	Total Number Of Members	Total (000 Litre)	Daily (Average 000 Litre)
1	2	3	4	5
Dharni	12	494	N.A.	N.A.
Chikhaldara	32	1208	233	0.64
Anjangaon Surji	19	676	6	0.02
Achalpur	44	1104	238	0.65
Chandurbazar	68	3455	1306	3.58
Morshi	33	893	588	1.61
Warud	30	892	N.A.	N.A.
Teosa	31	829	1947	5.33
Amravati	57	2590	2011	5.51
Bhatkuli	34	1221	2116	5.80
Daryapur	21	755	62	0.17
Nandgaon-Khande shwar	40	1118	5688	15.58
Chandur Railway	32	1010	1550	4.25
Dhamangaon Railway	23	875	44	0.12
Total	**476**	**17120**	**15789**	**43.26**

Dairy Development Co-Operative Societies Report : Yearly District : Amravati Reporting Year : 2010-11

Conclusion :

The efforts of the Dairy Co-operative Society in Chikhaldara taluka have greatly benefited the socio-economic development of the area. Firstly, local dairy farmers now rely largely on dairy cooperatives. The cooperative has helped farmers increase their income and productivity by providing access to modern technology, veterinary care and training, among other essential resources. This empowerment has reduced poverty in the region, which has also raised the standard of living of dairy farmers. Second, by creating a reliable supply chain and marketing network, cooperatives make it easier for dairy farmers to access markets. As a result, fair prices for dairy products have been guaranteed and farmers now have an opportunity to expand their industries. As a result, the dairy industry has become a significant catalyst for economic expansion in Chikhaldara taluk, creating employment opportunities and promoting entrepreneurship.

Additionally, dairy cooperatives have enhanced community growth and social cohesion. Cooperatives have improved social relations and enabled information sharing and mutual support by fostering a sense of shared ownership and cooperation among dairy farmers. The cooperative has also invested in social welfare programs such as healthcare and education, which have improved the general well-being of the neighborhood. Finally, dairy cooperatives in Chikhaldara taluk are essential for the socio-economic growth of the area. The cooperative has improved the quality of life of local communities and laid the foundation for sustainable development by empowering dairy farmers, facilitating market access and fostering social cohesion. In the future, Chikhaldara taluka's socio-economic prosperity will further increase with continued support and investment in the dairy sector.

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Dr. Manoj Bhagat, Dr. Pravin Chandak
Dr. Sau. Aparna Patil, Dr. Sunil Chakave
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CONTENTS

PART A – ENGLISH LANGUAGE PAPERS

Sl.no.	Title and author	Page no.
1	Recent Trends in Higher Education in the Faculty of Sports and Physical Education | *Prof. Dr. Rajani Bhoyar (Gaikwad)*	1
2	Review on Comparative study of various foods found in Amravati City | *Saket Wankhede*	6
3	Innovative Teaching Tools For Blended Education | *Mr. Dhiraj Vilasrao Nimsatkar*	11
4	Higher Education and Indian Knowledge System (IKS) | *Dr.Ashwinkumar R. Rathod*	29
5	Impact Of Interval Training On Physiological Parameters In College Students: A Comprehensive Analysis | *Dr. Ajay S. Bonde*	33
6	Neocolonial Perspectives in Jamaica Kincaid's A Small Place | *Prof.Shailesh Lachamareddy Jittawar*	40
7	A Review : Hazards Of Polythene On Health | *V. P. Garule & Dr. A.M. Bhoyar*	44
8	A Critical Analysis of Pedagogies and Curriculum of the NEP 2020 | *Dr Rajesh Anandrao Ade*	48
9	A Functional Study of Various Executive Co-operative Societies in India with special reference to Maharashtra as recommended by the Prof. Vaidyanathan Committee | *Mr. Ganesh. G. Wankhade*	53
10	A Review on Wastewater Treatment Techniques | *Ghodile R.D.*	58
11	A Study on Awareness about the Impact of National Education Policy 2020 | *Dr. Deepak Dattatray Nilawar*	67
12	Chemistry and area of Application of e-skin | *A.P.Bhat,[1] P.S. Ghubde,[2] A.V.Kawalkar[3]*	70

13	IR spectroscopic analysis of leaf extract of *Acacia nilotica* | *Dr. Rupali Subhashrao Kaikade*	79
14	Adaptation in New Country of Female Protagonist in Willa Cather's Prairie Triology | *Dr. Madhuri Pravin Chikhalkar*	82
15	Study of the gender stereotypes depicted in *Wuthering Heights* by Emily Bronte | *Mr. Amar Tulshiram Balki*	85
16	Approaches In Teaching And Learning Marathi: Higher Education In India | *Anand U. Dhundle*	91
17	Artificial Intelligence in Higher Education: Challenges & Opportunity | *Dr. Devanand Sakharam Ambhore*	95
18	Used of artificial intelligence to accelerating pharmaceutical technologies | *Miss.Sonali Pundit Punde & Dr. Rajesh. J. Mandade*	105
19	AI a Revolutionary Tool in making English Language Teaching Easy | *Nilesh D. Autkar*	123
20	Study of Physicochemical parameters of soil samples from Akot region, District Akola, Maharashtra | *Atul V. Yadgire*	130
21	The Elements of Globalization on Indian Literature : Arvind Adiga's The White Tiger | *Ku. Goldie K Jambhulkar*	135
22	Challenges facing Teacher Education in Higher Education | *Dr. Ananda P Wadwale*	139
23	Commerce Education: Way to Bright Future | *Dr. Arpita H. Laddha*	144
24	Comparative Study of Nutritional Composition of Freshwater Prawn and Shrimp | *Dr. S. K. Parate*	150
25	Enhancing Ergonomics in Indian Kitchens | *Ujwala Tikhe Kandalkar*	156
26	Entrepreneurship & Leadership Capacity Enhancement | *Prof. Pandhari Rambhau Gore*	162
27	Co-relation of ABO blood group system and Susceptibility for COVID 19 among the local population of Nandgaon Khandeshwar | *Dr Gajendrasingh S Pachlore & Dr Mamta R. Chandrakar*	167

28	Review paper on conducting properties of PS-PMMA Incorporated with Silver nanoparticles for growing electronic and electrical field | *Chitralekha Anil Kolhe*	170
29	Analysing the Operational Efficiency and Environmental Practices of Yashwantrao Chavan Open University: A Clinical Study | *Daya D. Deshmukh & Dr. Dinesh W. Nichit*	181
30	Quality Assurance and Accreditation of Higher Education Institutes in India in the Light of Global Perspectives | *Ashish Haridasji Hore*	187
31	Impact of Privatization, Liberalization, and Globalization on the Indian Economy | *Dr. Shivcharan Laxman Kottewar*	192
32	Recent Trends in the Faculty of Commerce & Management | *Ku. Sakshi Pradip Deshpande*	199
33	Diversity and distribution of phytoplankton in Kurala Dam, Malegaon Tahsil, Washim (MS), INDIA | *Kishor S. Sawaikar*	203
34	Diversity of Amaranthaceae family plant species from Campus of M.S.P. Arts, Science & K.P.T. Commerce College Manora Dist. Washim (M.S.) India | *Shivdas R. Aher*	211
35	Synthesis And Characterization Of Some Chalcone Derivatives | *C. M. Shahakar*	215
36	A Study of assortment of Tax Assessment in Nagarpalika with special reference to Amravati District | *Dr. Dinesh Prabhakarrao Bele & Dr. Manoj M. Pimple*	221
37	New Trends In English Language Teaching And Learning | *Dr. Jyoti Dnyaneshwar Dhokale*	227
38	National Education Policy – 2020: Opportunities and Challenges | *Pradeep B. Zilpilwar*	233
39	Global Issues of Race in "Beloved" | *Dr.Pritee Deorao Thakare*	240
40	Higher Education in India: Emerging Issues and Challenges | *Dr. Priti P. Gawande*	244
41	Recent Trends in Higher Education in the Faculty of Sports & Physical Education in India | *Dr. Shrikant S. Mahulkar*	251

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Impact of Privatization, Liberalization, and Globalization on the Indian Economy

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Introduction

India's New Economic Policy aims to pave the way for globalization by promoting liberalization and privatization in the Indian economy. The Indian economy, which was earlier bound by rules and restrictions, is now breathing freely. And it is moving in step with the countries of the world , because "Economic globalization involves the process of connecting national economies with the international economy and this trade is proved by foreign direct investment , short-term capital flows , labor and human resources in general" is Globalization: It is a process under which different economies of the world are coordinated so that goods and services , technological capital and labor or human capital can flow between different countries. The four main aspects of globalization are an organ.

1. Lowering trade barriers so that goods and services can be exchanged without hindrance.

2. 2. To create conditions for free flow of capital between different countries.

3. Creating an environment where technology can flow freely.

4. To create an environment that allows for seamless flow of labor between different countries of the world.

In the Indian context , globalization means opening the way for foreign companies and corporations in the Indian economy , allowing foreign direct investment and removing obstacles , restrictions and barriers in their way , giving opportunities for Indian companies to set up joint ventures with foreign companies. The main meaning is to allow , remove quantitative and non-quantitative restrictions on trade , encourage privatization and liberalization. And globalization means connecting the Indian economy with the world economy , so that it can develop faster while competing with other countries of the world.

Liberalization

Meaning of Liberalization (Liberalization) Economic liberalization has two parts - first , opening to the private sector those industries which were previously reserved for the public sector and second , relaxation or liberalization of regulations and restrictions for the private sector. Thus , liberalization refers to the relaxation of government restrictions or liberalization of economic policies. Thus , liberalization refers to the

ISSN 2454-1974

relaxation of government restrictions on economic policies. When a government adopts a policy of trade liberalization , it means that it has removed tariffs and subsidies and other restrictions so that the country can have unimpeded import and export of goods and services. Adoption of policy means opening up to private. Give area to industries which were earlier reserved for public sector. The number of industries earlier reserved for setting up private sector industries has also been reduced to three. Now many rules and restrictions have been relaxed and various formalities have been eased. ' Liberalization ' and ' market-oriented economy ' Theoretically , liberalization and ' market-oriented economy ' are two different things. Conceptually , however, liberalization promotes a market-oriented economy. A market-oriented economy is influenced by the development of market demand and supply forces and no restrictions are imposed on producers by the government. When the policy of liberalization is adopted, the role of the government in the economy gradually diminishes. Private entrepreneurs decide what to produce , how much to produce and for whom to produce. The producer class takes various decisions depending on the supply and demand forces in the market.

Need and Objectives of Liberalization Policy

1. It creates a competitive industrial environment.

2. The following objectives lie behind the adoption of liberalization policy.

3. Foreign investment is encouraged.

4. Resources are used properly.

5 Industrial development is promoted.

6. Helps in globalization of economy.

7. Improves domestic production system.

8 Employment opportunities have intelligence.

9. Improves people's standard of living.

Liberalization Policy in India-

The policy of liberalization adopted in India can be divided into two parts

1. Mild Liberalization Policy (1985 to 1991) The era of liberalization started in 1985 under former Prime Minister Rajiv Gandhi . Under this liberalization policy following steps were taken in the country

(**1)** In March **1985**, the government announced exemption of **25** large industries from licensing. (**2)** ' M. R. 22 industries were exempted from taking license under TP and FERA and MR Tea.

ISSN 2454-1974

P. The capital investment limit of the company was increased from Rs.20 crores to Rs.100 crores.

(**3)** In June **1985, 82** pharmaceutical companies were also DE-licensed.

(4) The capital investment limit for the development of small scale industries was increased from Rs.20 crores to Rs.35 crores. This limit has been raised to Rs 45 crore for ancillary industries .

(5) **(** 5) 100% export oriented units were completely exempted from licensing.

continued more or less during the period 1985-91 . Various incentives and concessions were given to the industrial units of the country , but the expected success in industrialization and economic development could not be achieved. So the country

The Liberalization Policy was announced with a fundamental change in India's economic and industrial policy , which gave a new direction to the process of liberalization , privatization and globalization in the country.

2. Deep Liberalization Policy (Post 1991 Period) The New Economic Policy introduced by Narasimha Rao's government in 1991

It was announced that the process of liberalization has been adopted in the fields of industrial , trade , economic , financial etc. Several steps were taken to compete in the international market , to connect the Indian economy with the global economy and to promote the process of privatization in the country's economy.

Apprehensions about liberalization policy

The following doubts are often expressed about the economic liberalization policy.

(**1)** Liberalization policy has increased foreign investment in India but foreign companies mostly invest in the same sector. Where the profit margin is high. Here the companies are more conscious about their profits rather than keeping the interests of the country in mind.

(2) Due to reduction in import duties and removal of quantitative restrictions , goods produced in the country will start coming into the country. Our industries will not be able to compete with the big foreign companies and will gradually shut down and eventually the country's industries will be taken over by foreign companies.

(3) Government of India is following the policy of liberalization under the pressure of World Bank and International Monetary Fund , which is not in the interest of developed countries.

Privatization

Meaning of Privatization: Privatization refers to the policy by which government ownership of an enterprise is changed to private ownership or the public management

ISSN 2454-1974

of a public enterprise is handed over to the private sector. In other words , privatization symbolizes the development of a new culture in society in which marketing , competition and efficiency become the guiding principles of economic decision-making. In England , through privatisation, buildings owned by local authorities were sold to the tenants who lived in them, and 50 per cent of the shares of state-owned companies were sold to private companies. The logic behind it was that it would increase economic efficiency .

Objectives of Privatization: The main objectives of privatization of economy are considered as follows.

1. Mobilization of financial resources for economic development.

2. Utilizing the managerial capacity and efficiency of the private sector.

3. Coordinating the productive activities of the private sector with the public sector according to national needs and priorities.

4. Reduction of external debt.

5 . Making the economy competitive.

6. To strengthen the process of import substitution by establishing new industrial units.

7. To increase productivity and operational efficiency.

8 Promotion of economic research and development programs for dissemination of appropriate technology , modernization of economy and rationalization of industries.

Privatization sector

Privatization is the general process of incorporating the private sector into state-owned enterprises. Following are the activities that fall under the field of privatization.

1. Contracting the company.

2. Buying a government company in whole or in part.

3. Privatization of management – management contracting , leasing or franchising arrangements.

Privatization involves three types of solutions:

(1) Remedies relating to ownership

Transfer of full or partial ownership to a private enterprise. This can happen in the following ways:

(a) Total Denationalization – It means transfer of entire ownership of public enterprises to private hands.

ISSN 2454-1974

(b) Joint ventures Transfer of public undertakings partly to private ownership. Private ownership It can range from 25 to 50 percent

Characteristics of globalization

Following are the main features of globalization

(Features of Globalization)

1. Under globalization , the country's economy is integrated with the world economy.

2. There is an uninterrupted flow of goods and services from one country to another.

3. Expansion of multinational companies.

4. The scope of national macroeconomic policies of the government has narrowed.

Arguments in favor of globalization

Proponents of globalization make the following arguments in its favor.

1. Globalization will encourage foreign direct investment , which will enable developing countries, who are not international borrowers , to access capital for their development.

2. Globalization will automatically make technologies developed by developing countries available.

3. Globalization leads to rapid expansion of knowledge , resulting in a developing world

Countries can improve their production and productivity levels. Thus it is helpful in achieving international level of productivity.

4. Globalization has expanded access for developing countries to export their products to developed countries It enables developing countries to obtain high-quality consumer goods , particularly consumer durable , at relatively low prices. Makes you eligible.

5 Globalization reduces the cost of transport and communication. It also reduces tariffs and increases gross domestic product The share of foreign trade as a percentage of production increases. Finally , it can be said that globalization can be considered as an engine of development , technological progress and productivity growth. This leads to poverty alleviation and modernization with expansion of employment.

People have huge doubts about globalization in India: **(1)** It will affect Indian industries badly. They will be left behind in the quality of goods produced by foreign firms **(2)** thus there will be a situation of closure of the industry. **(3)** Damage to industries

(**4)** Unemployment will spread among workers. (5) In future these foreign companies will exploit the country etc.

ISSN 2454-1974

Independence will be affected. Critics say that no nation can progress with the help of foreign multinationals . He himself You have to stand on your feet. Foreign investment should be made only in areas where Indian companies cannot invest. The economic policy emphasized making Indian industries more competitive , which required modernization of industries , i.e. adoption of modern technology and introduction of latest machines in large factories. But modernization is not easy for Indian industries. These are the main reasons for this.

1. Lack of capital: Here the owners have lack of capital and it is not easy for them to raise capital. The country lacks capital because savings are limited.

2. Workers' resistance: Workers in India are very afraid of modernization. He believes that with the advent of modern automated machines, there will be less need for workers . So there will be layoffs in their factories and it will affect them.

3. Lack of foreign exchange: Importing machines for modernization will require foreign exchange. There is already a shortage of foreign exchange. Nowadays he has to buy from the open market.

Factors driving globalization in India

Following are the major factors driving globalization in India.

1. ADVANCED TECHNOLOGY Advanced technology plays an important role in promoting globalization. Production of quality goods at low cost is only possible with advanced technology.

Can be affordable.

2. Liberal policies: Liberal policies adopted by various countries can pave the way for globalization.

3. Competition – Competition is a key feature of a capitalist economy. Competition forces companies to innovate There was a need to find a market and as a result new methods of production and sale were developed. of foreign companies

The fear of competition forced domestic companies to find their place in the world market and spurred globalization.

3. Experiences of developing countries: Developing economies that followed the process of globalization like China , Korea , Thailand , Hong Kong , Taiwan , Singapore etc. succeeded in attaining high economic growth rates. Inspired to do the same.

Conclusion

In conclusion, the impact of privatization, liberalization, and globalization on the Indian economy has been profound and far-reaching. While these reforms have spurred industrial growth, attracted foreign investment, and enhanced efficiency in certain sectors, they have also posed challenges in terms of employment generation,

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income inequality, regional disparities, and financial market stability. Moving forward, policymakers need to address these challenges effectively to ensure that the benefits of economic reforms are more inclusive and equitable across all segments of society.

Source

1. Based on the information available on the net.

窗体顶端

窗体底端

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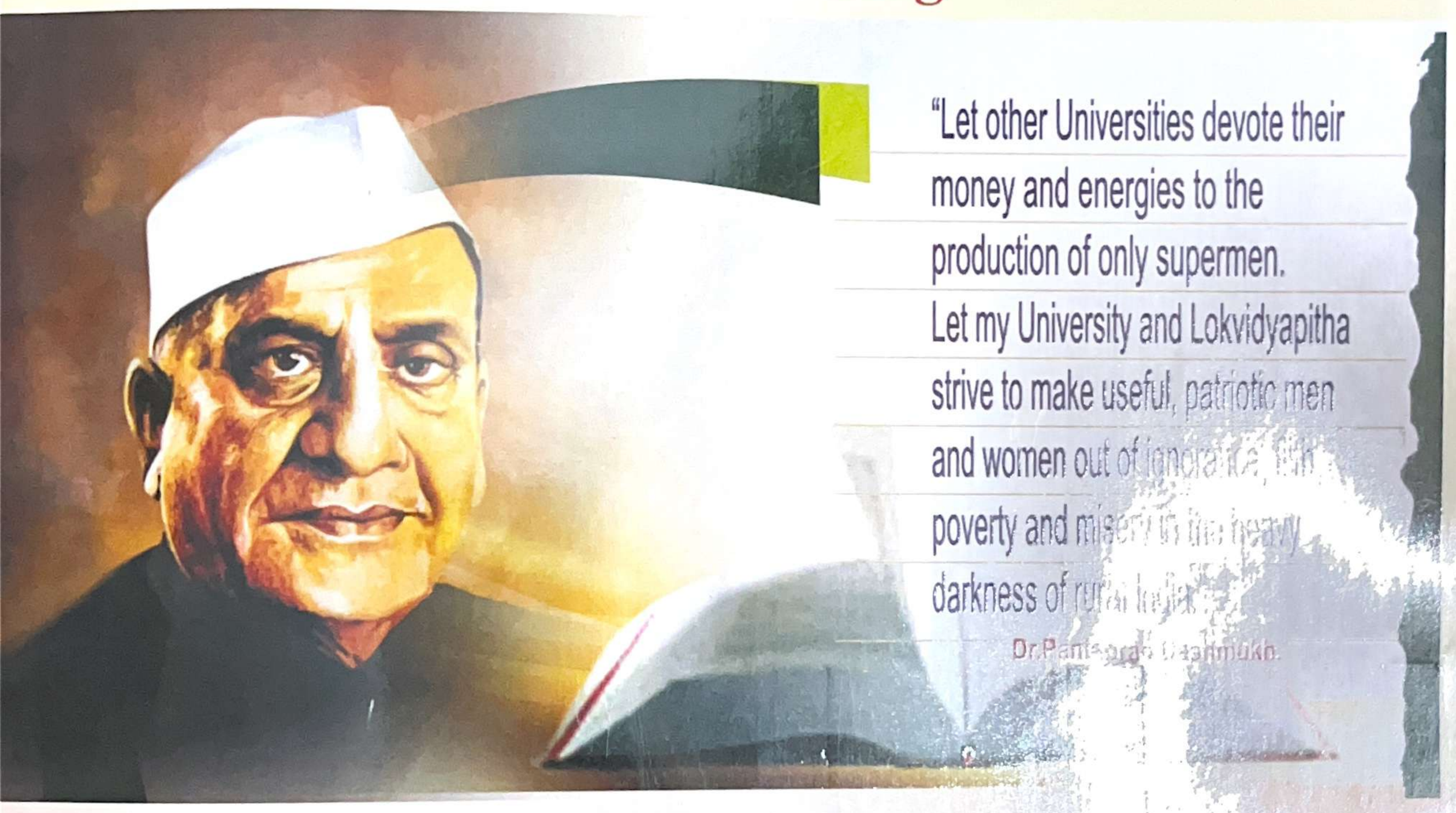
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Special Issue on

Contribution of Dr.Panjabrao Deshmukh in Nation Building



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INDEX

No.	Title of the Paper — Authors' Name	Page No.
1	Contribution of Dr. Panjabrao Deshmukh in Agricultural Development of India — **Dr.Shantaram Chavan**	1
2	Dr. Panjabrao Deshmukh's Work in the Constituent Assembly — **Dr.Shriram Yerankar**	7
3	Dr. Punjabrao Deshmukh: Champion of Education in Rural India — **Dr. Devendra S. Rangacharya**	10
4	The Great Visionary Dr.Panjabrao Deshmukh, Founder of Vikasit Bharat — **Dr.Smita Deshmukh**	15
5	Social Thinker : Dr. Panjabrao Deshmukh — **Dr. Gajanan S. Futane**	18
6	Dr.Panjabrao Deshmukh: A Radical Educationist — **Dr. Mrs. S. D. Thakare**	21
7	Dr. PanjabraoDeshmukh'sEducational Contributions and Achievements. — **Dr.Yogesh Dadarao Ugale**	24
8	The social apporach of Dr. Panjabrao deshmukh for vidhardhrabha region — **Dr.Harshal R.Nimbhorkar**	26
9	Social Reformer : Dr. Panjabrao Deshmukh — **Mr. Abhinav Gajanan Futane**	29
10	Contribution of Dr. Panjabrao Deshmukh as a Genuine Agriculturist — **Nisha Kale**	32
11	Dr. Panjabrao Deshmukh: The Doyen of Agricultural, Educational And Social Reforms In India — **Shriya Oke**	36
12	Dr. Panjabrao Deshmukh's Contribution in the field of Art and Literature. — **Dr.Vaishali Vijay Takode**	39
13	Krishi Ratna Dr. Bhausaaheb Punjabrao Deshmukh : His contribution in agriculture for Nation Building — **Dr. Kuldeep Mohadikar**	42
14	Political Thoughts And Work Of Dr.Panjabrao Deshmukh — **Dr. Maya S. Watane**	44
15	Dr. Panjabrao Deshmukh : Bharat Sevak Dal& Nation Building — **Rohini Arunrao Gaidhane**	47
16	Dr. Panjabrao Deshmukh's views and contribution in the field of education and its relevance in the modern era. — **Dr.Aparna Tulshiram Sarode**	49
17	DrPanjabRaoDeshmukh's Educational thoughts and his Social Contribution — **Dr Radhika Deshmukh**	53
18	Thoughts and Contribution of Dr.Panjabrao Deshmukh in the field of Agriculture — **Shri. Shivaji M. Kanfade**	56
19	Contribution of Dr.PanjabraoDeshmukh in Constitution Assembly and Nation Building of India — **Gajanan Vishwasrao Chopade, Dr. S.P. Chavan**	58
20	Economic Thoughts of Dr. PanjabraoDeshmukh — **Dr. Kavita S. Rodde (Makarwar)**	62
21	A Bio-bibliometric Study: Dr. Panjabrao Alias BhausahebDeshmukh — **Dr. Ms.Revati R. Khokale**	65
22	Dr. Panjabrao Deshmukh: Architect of Educational Empowerment & Social Change — **Dr. Archana Bobade**	71

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Contribution of Dr. Panjabrao Deshmukh in Agricultural Development of India

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Abstract

Dr. Panjabrao Deshmukh India's first Agriculture Minister contributed for India self-sufficient in food and cultivation. He also worked for progress in agriculture sector for economic development. Dr. Panjabrao Deshmukh was a realistic leader who devoted his entire life for the sake of downtrodden, labourers, rural citizens and farmers.Dr. Panjabrao Deshmukh is one of the realistic thinkers of the country. Dr. Panjabrao Deshmukh worked in the important field's like's education, agriculture, Social reformer, member of the Constitution assembly of India, first Union Agriculture Minister and on various national and International Organizations. By the major contributions of Dr. Panjabrao Deshmukh there have been sea changes in the country due to the vision and work of realistic leader. Dr. Panjabrao Deshmukh was the versatile personality and contributed in the Nation Building work.

Keywords: Agricultural Development, Rural Development Agricultural Entrepreneurship, Indian Agricultural, Indian Economy, Agricultural Exhibition, Dr. Panjabrao Deshmukh, Realistic,

Introduction: Dr. Panjabrao Deshmukh was Straightforward and pragmatic leader. As a first Union minister of Agriculture Dr. Panjabrao Deshmukh made a revolution in agriculture by introducing world agriculture technology to Indian farmers Community. He believed on exchange of technology and organized world agriculture exhibition at Delhi. Eisenhower the U.S. President visited India for inaugurating the world agriculture exhibition on 11th Dec 1959. Dr. Panjabrao Deshmukh published circular letters of his ministry to update all the state and union Ministers, Department about agriculture development.Dr. Panjabrao Deshmukh took every effort for the welfare of labourers and farmers in the country. His commitments with rural peoples were strong and tried to uplift the rural people from heavy darkness of backwardness. India's first Agriculture Minister Dr. Panjabrao Deshmukh worked for making India self-sufficient in food and cultivation of progress in agriculture sector and land improvements, canal bunds. He also contributed for the construction of irrigation, seed, fertilizers and pesticides.He established agricultural colleges and universities across the country and the updated laboratory for research. The market was produced by the agricultural income market committee to get the right price for the farmers. To create farmers entrepreneur, use modern technology in agriculture, and organizing agricultural exhibitions of innovative technologies, machines, livestock, etc., by making the major experiments.Dr.Panjabrao Deshmukh encouraged establishment of agriculture universities all across the country, and gave extended huge support for agricultural education, agricultural research and related extension activities. He wanted to ensure that the final beneficiary of all this enterprise would be an ordinary farmer.He was elected thrice for the LokSabha. Dr. Deshmukh was selected by Nehru as India's first agriculture minister. He played an important role in the making of the Indian Constitution.He was the Leaders of the farmers and common people: He dedicated his talent and energy to the formulation and implementation of the policies that would bring prosperity to agriculture and the agriculturist. He established the Bharat KrishakSamaj and launched a campaign called Food for Millions in 1955. He introduced the Japanese method of rice cultivation in 1958 and organized the World Agriculture Fair in 1959. The fair was visited by dignitaries across the world, including US President Dwight Eisenhower, USSR President Nikita Khrushchev, Lord and Lady Mountbatten. Now a day Welfare of Labourers and Farmers In the era of globalization, India is facing the problem of farmer suicides. In spite of many packages, committees, suicides of farmers do not stop. The reason behind this failure is the lack of vision of the earlier government. Dr. Panjabrao Deshmukh while speaking on a welfare of labourers and farmers ,strongly appealed to establish welfare board for farmers on the line of social welfare board which will take care of farmers education, health and sanitation. He regrets that drafting committee of the constitution has not considered the problems of farmers in the country. He wrote a letter to Dr.Rajendra Prasad, Chairman of the Constitution Committee on 12 March 1948 to address the issues of farmers and lack of representation of farmers on the Constitution committee. He pointed out that the constituent assembly is dominated by non-farmer and in constituent assembly the

interest of poor farmers and labourers who are the real masses of India hardly get any place. In the presentpaper attempts have been made to emphasize the realistic views of Dr. Panjabrao Deshmukh in the fields of rural and agriculture development in which heworked and changed.

India is an agricultural country. The Indian economy is based on agriculture.Indian farming depends on nature. Monsoon's rain is an imbalance so that the income is difference; the result of the changing environment is going on. The rainfall of the rain is getting less. Dr Panjabrao Deshmukh laid the foundation for accelerating agricultural progress in India. He had a strong faith in science and technology as prime movers of change in farmers' fields. In order to highlight the importance of technology, he organized the World Agriculture Fair in 1958. This Fair was opened jointly by Gen Dwight D Eisenhower, then President of the United States and Pandit Jawaharlal Nehru, the Prime Minister of India. In order to give voice to farmers in policy making, Dr Panjabrao organized the Bharat KrishakSamaj, which is still functioning effectively. In his monthly letters to the Agriculture Ministers of State Governments, Dr Deshmukh described in precise terms the action that should be taken during that month to assist farm families to manage the monsoon. He used to stress that the monsoon and the market are the two major determinants of a farmer's wellbeing.

Agriculture is the backbone of our Indian economy. Agricultural development is a requirement of our national prosperity. Agricultural growth is critical for improving food security, most immediately by increasing food production and availability. Agriculture helps to grow crops and livestock for food and industrial raw materials and is the main source of calories for the world's population. The availability of food is a necessary but not a sufficient condition to assure food security. The traditional role of agriculture in producing food and generating income is fundamental, but agriculture and the entire food system – from inputs and production, through processing, storage, transport and retailing, to consumption – can contribute much more to the eradication of malnutrition. Following the green revolution whose thrust was on increasing production through the productivity pathway, agriculture evolved in the decade of the 1970s to include environmental and equity considerations. Sustainable development issues came to the forefront, partly in response to concerns associated with the Green Revolution such as the overuse of agricultural chemicals, the depletion of scarce water resources, and the neglect of farmers and communities in policy-making processes. These concerns encouraged a shift away from a narrow focus on increasing staple food productivity to a more complex perspective on agriculture and rural development. Efforts were accelerated to make the Green Revolution not only more sustainable but more pro-poor. New policies, programs, and investments were specifically designed to integrate rural communities into decision making processes about their own agricultural and rural development as a way of addressing sustainability along with equity issues. There was growing attention on land reform, especially the equitable distribution of land with secure property rights, access to credit and financial services, and programmes more geared toward small-scale farmers. We should attend to six key areas to safeguard the stability and sustainability of agricultural production in India. 1)We should take steps to ensure that good farm land is conserved for agriculture. 2)Irrigation security will have to be ensured through integrated attention to harnessing rainwater, river and other surface waters, ground water, treated waste water and sea water. Rain water harvesting should be made mandatory both in rural and urban areas. 3)Technology and inputs need to be custom-made to the agro-ecological and socio-economic conditions under which farmers work. 4) Farmers should receive appropriate credit and insurance support. Credit should be made available at lower interest rates as recommended by the National Commission on Farmers (NCF). 5) Procurement at the minimum support price (MSP) is the greatest incentive to farm families. The MSP should be C2 plus 50 per cent as recommended by NCF. 6)There is need to give the power and economy of scale to small holders.

Jawaharlal Nehru told in 1947, "Everything else can wait, but not agriculture," and that message is even more relevant today. we convert LalBahadurShastri's slogan "Jai Kisan" into a reality and focus our energies on realizing the goal of a hunger and malnutrition free India. Above all, the lead given by Dr Panjabrao Deshmukh in the area of bridging the gap between scientific know-how and farmers' do-how should be followed. Dr Panjabrao Deshmukh was a great advocate of the technological up gradation of small farms and he organized an "Atoms on the Farm" exhibition at the World Agriculture Fair in 1958, in order to raise awareness on the relevance of nuclear technology in scientific agriculture. Agricultural Universities and Biotechnology Research Institutes should follow Dr Panjabrao Deshmukh's example and organize in various parts of the country exhibitions on the theme "Molecules

on the Farm" to bring out the uncommon opportunities opened up by new genetic combinations for facing the challenges of climate change, environmental degradation and malnutrition.

Dr.YashwantThorat expert in the field of agriculture expressed his thoughts in the 28th Convocation of Dr Panjabrao KrishiVidyapeeth, Akola in his Convocation Address. Agricultural growth continues to impact the overall performance of the Indian economy in asignificant way. Therefore, ifwe want to reach our GDP growth targets, we must achieve and sustain a high average growth inagriculture.But the fact is that growth in the agriculture sector, whenviewed from the long term perspective, has been both low and unstable. However, interestingly, thoughthe contribution of agriculture to the GDP i.e., to the economy as a whole has fallen over time,the number of people engaged in or dependent upon agriculture continue to be constant at around60% of our population. The implication of a relatively low growth rate in agriculture, low outputand a constant population dependent upon the sector is that the income gap between the workerin the manufacturing or service sector and the farmer, particularly the small and marginal farmercontinues to increase.The unpredictability of agriculture is due to factors such as climate change, global warming, wield life animals, insects attacks, non-availability of funds at proper time, high price of fertiliser, over-dependence on themonsoons, fragmented land holdings, low investment and consequently declining productivity,absence of coordination between production, procurement and prices of commodities, highwastages, lower processing and, as a result, inadequate flow of credit. Due to this agricultureis identical with risk and uncertainty. Crop failure on account of adverse weather condition iscommonplace to Indian agriculture. It affects the farmer's income and consequently, his abilityto meet day-to-day family expenses to pay his debts in time. Expert of the field of agriculture suggested one way to mitigate the risk faced by farmers is to provide them with aneffective weather insurance scheme. Such a scheme would benefit farmers across states and alsoserve as an effective check on the trend of increasing obligation of farmers in the event of acrop failure.

On the other had the other sectors – manufacturing and services - are able to attract higherinvestment as compared to agriculture & allied sector over the Plan periods resulting in growthdisparities. Though this is in line with the falling share of agriculture in the overall GDP, and inconformity with the development process observed elsewhere in the developing world, yetkeeping in view the high population dependent on agriculture for sustenance, there is need tosubstantially increase investment in agriculture.Investment is of two kinds - public and private. While public – i.e., government - investment inagriculture is life-threatening and has a dynamic, impact on private sector investment, it forms nomore than about 20 % of the total investment in agriculture. An important issue often debated is whether agricultural output is – and will be - in a position toaddress our consumption and food security requirements? An in-depth analysis of demand andsupply in Indian agriculture over the long term indicates that from 2021 onwards, the increaseddemand for food due to population growth and rising per capita income is likely to exceed thesupply of cereals, pulses, edible oil and sugar. This demand can only be met by bringing aboutproductivity increase in food crops because though the yield of major crops has grown over time,it is still low as compared to other major agriculture commodity producing countries in theworld.On the structural side, the first point is that Indian agriculture is increasingly becomingcharacterized by small farmers. Disintegration and subdivision have been progressively increasing.The distortion in the distribution of land holding coupled with thepredominant share of small farmers, points to the need for promoting institutional arrangementsdesigned to ensure that growth along with its diversification, benefits the small and marginalfarmers. About the irrigation the condition is not good. Groundwater irrigation is presently the largest source of irrigation. However, it suffers fromover-exploitation in most states. Excessive dependence on groundwater for irrigation has severalimplications – which we can ill afford – such as declining groundwater tables, drying up ofwells, rise in well and pumping depths and salinity entrance.Greater integration of the agricultural sector with the overall economy and the integration of theIndian economy with the global economy have brought in their wake certain challenges andconcerns. Three factors namely, globalization, an expanding middle class and diversification ofthe Indian food have led to an increasing interest being taken by corporates in agricultureas a source for raw material for "agriculture value chains" and the focus is now increasingly onmarketing of produce. As a result, marketing systems at various levels are gearing up to adoptbest practices in procurement, storage, transport, packing and processing of food products. Foodsupermarkets have become a reality and it is expected that they will play an increasinglysignificant

role in the years to come as suppliers of quality farm produce delivered in modernformats to the growing urban sector.Dr.SunitaKalakhe explained in her research paper titled - Need of Agricultural Entrepreneurship training to Students in India: Special reference to suicide effected region of Maharashtra, which was published in theJETIR November 2021, Volume 8, Issue 11 www.jetir.org (ISSN-2349-5162). Due to getting a low price of the commodity, the budget of the farmers is being created, the deficit. Agricultural business has created a need to make an agricultural business in order to afford the farmers in such a situation, because the farming is low, due to lack of affordable, and there is no other option for farmers. In the changing environment and the government's empowerment, liberalization, privatization policy is decreased. By changing the form of farming in the changing conditions, farmers, farmers need to make a little change in the device of income. If this change is accepted by becoming agricultural entrepreneurs and it is necessary to learn the process of production, marketing etc.

India's first agriculture ministers Dr.Pranjabrao Deshmukh was studied the progress of the agricultural sector in Japan, America and Europe, but the farmers will not be able to commit suicide. Not only thought that progress is not financially progress, but in that case, the agricultural exhibitions of technology and farming in agriculture and establishing new research and agricultural universities, through the agricultural conference council. He has shown the new experiment from the exhibition and training of the new experiment and in true sense. The Maharashtra Government has set up a mission for promoting Organic Agriculture in the state by passing a Government Resolution on 16th October 2018 through the state department of Agriculture, Animal Husbandry, Dairy Development and Fishery. The mission has been named Dr. Panjabrao Deshmukh Organic Farming Mission - Akola. The Mission will help the farmers in production, certification, processing and marketing of farm products such as fruits, vegetables, pulses and grains, which would be free from chemical fertilizers, pesticides and insecticides. The mission is being implemented in the vidharbha region namely six districts Akola, Amravati, Buldhana, Wardha, Washimand Yavatmal. The mission has its headquarter (Project Management Unit) at Akola and District Management Units at respective six districts. The mission will focus grass root level activities through selected Service Providers for six districts. A budgetary provision of Rs. 100 cores has been made by the state government for the mission to be implemented in four years period. The aim of the mission is to achieve increased productivity through organic farming and sustainable, low external agriculture input with a reduction in production costs and establish Organic produce marketing chain /linkages which is expected to result in increased household incomes and improved food security with nutrition values. This is for promoting low cost organic farming approach with the Biodynamic Agriculture Systems very well accepted in Maharashtra.

Some issues need to be focus in the present times that are

Rural – urban range: In addition to the structural issues discussed, other changes are also taking place at the groundlevel. For example, the hitherto identifiable distinction between the rural and urban sectors hasgradually given way to a sort of "rural – urban range" characterized by the watermark of theservices sector. This transformation is, in part, captured in the shift in the consumption pattern inthe rural areas because rural India is now an important constituent of in the domesticconsumption on account of the population residing there, its share in national income,expenditure and savings.

Mechanics of procurement and release of food grains: Agricultural growth strategy has for a long time focused mainly on the production phase. In thecontext of food grains policy, concerns have been raised regarding the simultaneous presence ofhigh food inflation and large food grains stocks in our granaries. It has been argued that, increating a better food grains policy, it is imperative to look at the entire system of food grainsproduction, procurement, release and distribution. Thus, besides improving storage facilitiesthere is a need to redesign the mechanics of procurement and release of food grains to the marketto ensure that the impact on prices is in the desired direction. Marketing conditions also need tobe improved.

Minimum support price: Minimum Support Price characterised by a number of equity driven advantages, has also led toover production of food grains despite rapidly increasing food grains stocks with FCI. It hasstifled diversification to other remunerative and market demanded crops as a result of whichthere is a need to review the food management policy. Instead of maintaining high levels ofbuffer stocks, an alternative strategy could be to restrict the open procurement of food grains tothe minimum required for food security purposes or to bring about a balanced reduction inprocurement which would

lead to both crop diversification and significant savings for the publicexchequer. The savings, thus affected could be used for creating a targeted and better-managedsafety net for the poor or for creation of infrastructure facilities.Dr.Panjabro Deshmukh initiated as an Agriculture Minister of India at that time, but in future after him policies are not frame in the favour of farmers.

Agricultural exports: India has graduated from being an imported-food-dependent country to a self-sufficient nationand even a net exporter of cereals. The agricultural export basket is quite diversified and some ofthe billion-dollars-plus exports are that of rice, high value commodities such as fish, cotton, andfruit and vegetables. However agricultural trade in India is often subject to "stop-go" policies onaccount of food security concerns. There is, therefore, a need to work out strategies to increaseexports and decrease the gap by improving post-harvest technology and agriculturalproductivities, increasing the irrigation potential and encouraging farmers to adopt least-costproduction methods through strengthening of extension services.

Dry land Agriculture: With 65% of agriculture in India being undertaken in dry land and resource poor regions requiresa completely different orientation and approach to such areas. This is especially critical in thecontext of food security. Even with full development of water resources in the country, it isprojected that about 45-50% of net sown area will always remain rainfed. While the Greenrevolution by-passed rain fed areas, the productivity growth is declining in irrigated agriculture,which is a matter of concern for sustaining and augmenting food grain production in the countryin the coming years. In my mind there is no alternative but to harness the vast potential of rainfedagriculture for contributing to the country's food and livelihood security.

Need of Agricultural Entrepreneurship: The farming was an affordable near about fifty years ago because the cost of the expense in agriculture is very low, the seeds of seeds are being prepared and the number of housing persons was not spent. But today due to a large amount of expenditure in agriculture, farming has not been affordable because there is no increase in farming. Since the number depending on agriculture is large because more than 55 % community is based on farming. The country's economic development will also be seen only if per capita income increases. It requires entrepreneurship development program for providing information about new experiments for prosperity, to visit agricultural business and consulting the expert guide, to acquire technology. These programs are being grown in a large level.

CONCLUSIONS: Dr Panjabrao Deshmukh laid the foundation for accelerating agricultural progress in India. He had a strong faith in science and technology as prime movers of change in farmers' fields. Dr. Panjabrao Deshmukh was a realistic leader who devotes his entire life for the sake of downtrodden, labourers, rural citizens and farmers. There have been sea changes in thecountry due to the vision and work of realistic leaderDr. Panjabrao Deshmukh.Dr. Panjabrao Deshmukh was one ofthe realistic Thinkers of the country.Dr. Panjabrao Deshmukh worked in the important field'slike's education, agriculture, Social reformer, member of theConstitution assembly of India, first Union Agriculture Minister and on various national and International Organizations. Dr. Panjabrao Deshmukh was the versatile personality and contributed in the Nation Building work.Dr.Panjabro Deshmukh had vision toNeed of Agricultural Entrepreneurship, Minimum Support Price; need to work out strategies to increase exports. He initiated many projects as an Agriculture Minister of India at that time, but in future after him policies are not frame in the favour of farmers. Expert of the field of agriculture suggested one way to mitigate the risk faced by farmers is to provide them with an effective weather insurance scheme. Marketing conditions also need to be improved.Dr. Panjabrao Deshmukh encouraged establishment of agriculture universities all across the country, and gave extended huge support for agricultural education, agricultural research and related extension activities. He used to stress that the monsoon and the market are the two major determinants of a farmer's wellbeing.

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INDEX

Sr. No.	Title	Author / Researcher	Page No.
1	Ram Mandir a Place of Eco- Religious Tourism in Ayodhya: A Comprehensive Study	Dr. Sanjay Mishra Dr. Mahesh Lavate Dr. Vishesh Shrivastava	1-8
2	Study of Invasive Plant Species Character of Water Hycanith from Ambazari Lake of Nagpur District, Maharashtra (India)	Mrs.Neha D.Gajbhiye Dr.Ujwala Ramesh Kokate	9-13
3	**साहित्यरत्न अण्णाभाऊ साठे यांच्या साहित्यातील संवादशास्त्रीय दृष्टिकोन**	**प्रा. डॉ. दिनकर माने भानुदास लक्ष्मण दोबाले**	14-17
4	Changing Agricultural Landuse Pattern in Jalna District	Dr. Sakhare S. N.	18-21
5	A Study of Literacy Pattern in Aurangabad District	Dr. Bhagwan Markad	22-25

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Study of Invasive Plant Species Character of *Water Hycanith* from Ambazari Lake of Nagpur District, Maharashtra (India)

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Abstract:

Nagpur district lies between 20º35' and 21º44'N and 78º15' and 70º40'E in the plain to which it gives its name at the southern base of the Satpura hill. Its area is 3840 square miles. Nagpur is the third-largest city of the Indian state of Maharashtra. Plants that do not occur naturally in a region but proliferate in the area they have been introduced into a cause of several negative impacts in these new habitats are called invasive plants. The invasive plants species are naturalized plants that produced reproductive offspring, often in very large numbers at considerable distance from parents plants. In this article, efforts are taken to gather the information of character of *Water hycanith* which is the invasive plants species has great impact on the Ambazari lake of Nagpur District, Maharashtra.

Keywords: *Invasive plants species, Water hycanith, Amabazari lake.*

Introduction:

Nagpur is named after the great river Nag which flows through the city. The old Nagpur city (today called Mahal) is situated on North banks of the river Nag. The suffix pur means 'city ' in many Indian languages.

Nagpur city is dotted with natural and artificial lakes. The largest lake is Ambazari lake. Ambazari lake is situated near the southwest border of Nagpur , in the state of Maharashtra. The Nag river of Nagpur originates from this lake. This was built in the year 1870, under Bhosale rule, for supplying water to the city. This lake is surrounded by Mango trees, gaining the name Ambazari as 'Amba' means 'Mango' in Marathi. The lake also has a garden located just beside it known as Ambazari garden. The garden was established in 1958 on an area of 18 acres of land.

Ambazari lake is not just an ordinary lake .It is one of the largest artificial water bodies in the city of Nagpur. The lake receives water from the nearby Ambazari dam in addition to several small streams and rivers flowing within the lake itself.

The Flora surrounding it is extensively diverse with many species unique to this part of the country being observed. There is also a vegetation like trees and shrubs. There is a vast array of beautiful plants, from lotus flowers blanketing the lake's surface to lush grasses growing its banks. The lake also features plenty of trees, such as their state tree- the silk cotton tree as well as numerous palms and tropical plants. The visitors will delight in the biodiversity of this special place.



Characteristics of Water hyacinth species:

Pontederia crassipes (formerly Eichhornia crassipes),commonly known as common *Water hyacinth* is an aquatic plant native to South America, naturalized throughout the world, and often invasive outside its native range. It is the sole species of subgenus Oshunae within the genus Pontederia . Anecdotally, it is known as the **'terror of Bengal'** because it is an exotic shrub which is growing at an alarming rate on the surface of water body, due to its invasive growth tendencies. It inhibits the growth of other aquatic organism due to cut down of light and lack of oxygen.

Water hyacinth is a free-floating perennial aquatic plant (or hydrophyte) native to tropical and subtropical South America. With broad, thick, glossy, ovate leaves. Its may rise above the surface of the water as much as 1m(3ft) in height. The leaves are 10-20cm (4-8 inches) across on a stem, which is floating by means of buoyant bulb-like nodules at its base above the water surface. They have long, spongy bulbous stalks. The feathery, free hanging roots are purple- black. An erect stalk supports a single spike of 8-15 conspicuously attractive flowers. Mostly the flowers is lavender to pink in color with six petals. When the flower is not in bloom, *Water hyacinth* may be mistaken for frog's bit (Limnobium spongia) or Amazon forgbit (Liimnobium laevigatium).

One of the fastest growing plants known, *Water hyacinth* reproduce primarily by way of runners or stolons, which eventually from daughter plants .Every plant additionally can produce thousands of seeds each year. These seeds can remain viable for more than 28 years. The common *Water hyacinths* (Pontederia crassipes) are vigorous growers and mats can double in size in one to two weeks. In terms of plant count rather than size, they are said to multiply by more than a hundred folds in number in 23 days.

In their native range, the flowers are pollinated by long-tongued bees, ant plants can reproduce both sexually and clonally. The invasiveness of the hyacinth is related to its ability to clone itself, and large patches are likely to all be part of the same genetic form. It has three flowers morphs and is termed" **tristylous**". The flower morphs are named for the length of their pistils: Long(L), Medium(M),and Short(S).In the introduced range ,the M-morph prevails, with the L- morph occurring occasionally and the S-morph is absent altogether. Geographical distribution of these floral morphs indicate that founder events have played a prominent role in the species worldwide spread.

Impacts of *Water hyacinth* on the lake:

"*Water hyacinth* has a variety of negative impacts."

Once it introduced into freshwater environment, it forms dense, impenetrable mats which clog waterways, making boating, fishing and almost all the water activities is

impossible. These plants also reduces biodiversity by crowding out native plants at the water's surface and below. It blocks light and smothers beds of native submersed and vegetation. The *Water hyacinth* has since spread prolifically , due to a lack of natural predators, an abundance of space, agreeable temperature conditions, and abundant nutrients ,including increasing heavy metal pollution in the lake. Their mat-forming nature severely impacts biodiversity by preventing the entry of sunlight and oxygen to the bottom of water. Their growth prevents the natural flow of water in irrigation channels, obstructs smooth navigation and interferes with hydroelectric power generation. These plants also result in depletion of the dissolved oxygen levels in the water. The high oxygen demand can deplete the oxygen levels in the water, which is essential for fish survival. Consequently, many fish may perish due to insufficient oxygen. Furthermore, *Water hyacinth* can block sunlight from penetrating the water, hindering the reproduction process of fish and disrupting their habitats. The decaying process depletes the amount of dissolved oxygen in the water.

Effect of *Water hyacinth* on Human and Animal:

The toxic principle of these plants is very concentrated in the bulbs(verus the leaf or flower), and when ingested in large amounts, can result in severe clinical signs. Severe poisoning from *Water hyacinth* is often seen when dogs dig up fleshy planted bulbs or having access to a large bag. *Water hyacinth* bulbs have been known for years to cause skin irritation, contact eczema and respiratory irritation in humans. Piirila et al.(1998) were the first to document occupational asthma caused by hyacinth. Birch twig and marguerite most frequently induced symptoms, followed by strongly smelling flowers .Unspecific irritants caused symptoms in 98% of the asthmatics and in 67% of patients with rhinitis.

"If we handle *Water hyacinth* bulbs, they can irritate your skin." because the bulbs contain oxalic acid, which is also found in rhubarb.

Materials and Methods:

Water hyacinth is a floating aquatic plant which is most invasive species in the world. *Water hyacinth* is also known as one of the fastest growing plants. *Water hyacinth* plant is control by Physical, Chemical and Biological methods.

Physical Methods: In physical method the manual extraction is more effective than chemical and biological method for the removal of *Water hyacinth*. In Ambazari lake the manual work is done to remove the weeds, but yet it is not completed as the lake is vast.

Chemical Method: In Chemical method the spraying of chemical herbicides such as Glyphosate, Imazamoxi,2,4-D and Florpyrauxifebenzyl are found more effective in reduction of *Water hyacinth*. It found more harmful method for the micro-organisms and other non-target plants that provided habitat for the other organisms. It's also effects to the fish production.

Biological Method: Biological control methods agents require time for their impact to be observed but once established, populations usually remain present. The biocontrol agent will never completely eliminate, but it can reduce the plant below problem levels. While the development and implementation of biological controls take time, the long-term cost in management is often significantly less than other control measures and less harmful to the environment. Most of the above water parts of the plants are killed by forst during the winter. Natural increase and decrease of the weed will still occur, possibly seasonally or over a number of years, but level should be lower than before. The occassional massive seasonal flood, now largely tempered by dams, could have a large impact on plant and natural enemy populations.

Sample Collection:

Water hyacinth plant samples were collected from the Ambazari lake in October 2023 and(at site 3x3m^2 ,approx.1m deep,1.5m from the bank).The plants were transferred to the laboratory in polyethylene bags. Plants of similar shape, size (weight of each plant,200± 20g wet mass) and height(roots 21-23cm,aerial parts 25-26 cm) were selected and washed several times using tap and distilled water. The plant were rinse properly to remove all the

debris from roots and leaves. This plant is then preserved in a glass jar. The jar contain 40% formalin and distilled water(i.e it should be mixed at a ratio of nine parts water to one part formalin). The plant is preserved here for a long years for the study of their scientific characteristics.



Conclusion:

The Nagpur Municipal Corporation has been consistently removing *Water hyacinth* from Ambazari lakes, but lakes is still plauged by weeds .The NMC has identified that the weeds flows in from Wadi and MIDC areas, and they have formed a committee of experts to address the pollution source. The solid waste management department has removed 940 truckloads of weeds and used the Jaldost airboat system to aid in the task. To review committees have been formed to tackle the challenge, with the involvement of the MPCB, Neeri and other experts.

The flooding of *Water hyacinth* in Ambazari lake has now become a matter of concern for the civic body as well as for citizens. After cleaning the weeds flow the overflow spot of the lake, Nagpur Municipal Corporation (NMC) ,started removing weeds from other parts of the lake with the help of small boats. Ambazari lake overflowed recently in monsoon season due to heavy rains in city and huge amount of weeds obstructed the flow of water from the over flow side of the lake. According to environment experts, *Water hyacinth* also reduces biodiversity by crowding out native plants at the water's surface and below. It also degrade water quality by blocking the air-water interface and greatly reducing oxygen levels in the water, eliminating underwater animals such as fish."These weeds will never be eradicated completely, but management is necessary to control its rapid growth, as the mat it forms can double their size in 6-8 days."Water hyacinth plants should be control as it will affect the biodiversity of the ecosystem of lake.

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Effect of Solvents on the Ultrasonic Velocity and Allied Parameters of Nifedipine Drug in Different Mixed Solvents at 300 K

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ABSTRACT

The scientific investigations in the field of ultrasonic velocity measurements in drugs solutions in various binary solvents mixture is carried out. The measurements were performed with ultrasonic interferometer (Mittal Enterprises, New Delhi) at a frequency of 2MHz with a tolerance of ± 0.005%. The density, viscosity and ultrasonic velocity for Nifedipine drug have been investigated by experimental procedures in order to understand the effect of ion-ion interaction and influence of ions on solvents structure in different medium at 300K in the concentration range of 0.02 to 0.06 mol dm^{-3}. In this present work various acoustical parameters such as apparent molar compressibility (φ_k), apparent molar volume (φ_v), intermolecular free length (L_f), adiabatic compressibility (β_s), specific acoustic impendence(Z),etc. have been evaluated. Ultrasonic studies provide valuable information in understanding the molecular behavior and intermolecular interactions of Nifedipine drug in different solvent mixtures. The variation of these acoustic parameters is explained in terms of solute-solvent molecular interaction occurring in drug solutions.

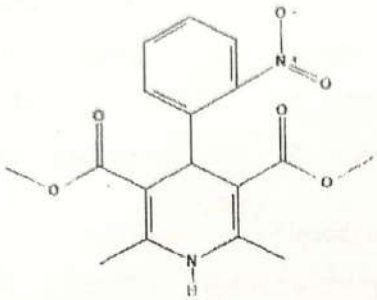
Introduction

Recent developments have found use of ultrasonic measurements in medicine, engineering, industry and agriculture[1-2]. Solvation describes the interaction of solvent with dissolved molecules. Both ionized and uncharged molecules interact with solvent, strength and nature of this interaction influence many properties of the solute as well as influencing the properties of the solvent such as viscosity and density. Ion-solvation is the back bone of solution chemistry [1-2]. Ultrasonic waves and related thermodynamic parameters provided valuable information about the structure of solid. The measurement of ultrasonic velocity has been adequately employed in understanding the nature of molecular interactions in pure liquids[3-6] and liquid mixtures[7-8]. Ultrasonic propagation parameters yield valuable information regarding the behavior of liquid systems, because intramolecular and intermolecular association, dipolar interactions, complex formation and related structural changes affect the compressibility of the system which in turn produces corresponding variations in the ultrasonic velocity. The acoustical and thermodynamical parameters obtained in ultrasonic

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study show that the ion solvation is accompanied by the destruction or enhancement of the solvent structure[9-12]. Excess thermodynamic properties of liquid mixtures are of great interest to conveniently design industrial processes and also to provide valuable information on the molecular interactions required for optimizing thermodynamic models. When two or more liquids are mixed there occur some changes in physical and thermodynamic properties because of free volume change, change in energy and change in molecular orientations. Derived thermodynamic and acoustical parameters like internal pressure, free volume and acoustic impedance are of considerable interest in understanding the intermolecular orientations in binary liquid mixtures[13-14]. Excess thermodynamic properties of mixtures are useful in the study of molecular orientations and arrangements[15-16].

For the present study Nifedipine drug is selected and its chemical structure is



Dimethyl 2, 6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

The Nifedipine inhibits the entry of calcium ion by blocking these voltage-dependent L-type calcium channels in vascular smooth muscle and myocardial cells. It works by affecting the movement of calcium into the cells of the heart and blood vessels. As a result, Nifedipine drug relax blood vessels and increases the supply of blood and oxygen to the heart while reducing its workload. So, it was found important to study ultrasonic and thermodynamic behavior of the dugs which may lead to some new findings. The acoustic properties of Nifedipine drug have been studied in 40% Ethanol-water, 40% Acetone-water and 40% DMF-water solutions at 300K.

Experimental

Ultrasonic velocity measurements were made by using an ultrasonic interferometer (Mittal Enterprises, New Delhi) at a frequency of 2MHz with a tolerance of ± 0.005%. All the measurements were carried out at 300K.The temperature was maintained constant by circulating water from controlled water bath (accuracy ± 0.1^0C). For the present work ethanol, acetone and dimethyl formamide solvents used which are of AR grade and were purified by the usual procedure. Densities, viscosities and ultrasonic velocities were measured at 300K over a wide range of composition. Densities were determined by using 25ml capacity gravity bottle and digital balance with an accuracy of 0.0001g. The viscosities were measured by precalibrated Ostwald viscometer.

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Theory

Various Acoustic parameters such as apparent molar compressibility (φ_k), apparent molar volume (φ_v), adiabatic compressibility (β_s), specific acoustic impendence (Z), intermolecular free length (L_f), Limiting apparent molar volume (φ^0_v), Limiting apparent molar compressibility (φ^0_k) were determined using following relations.

1. Ultrasonic velocity $u = \lambda\upsilon$
   Where υ is the frequency of ultrasonic waves and λ is the measured wavelength of ultrasonic waves in solution.
2. Adiabatic compressibility (Newton-Laplace equation) $\beta_s = 1/ u^2_s \rho_s$
3. Apparent molar volume $\varphi_v = 10^3(\rho_0-\rho_s)/m\text{-}\rho_0 \rho_s + M/\rho_0$
4. Apparent molar compressibility $\varphi_k = 10^3(\rho_0\beta_s-\rho_s\beta_0)/m\text{-}\rho_s \rho_0 + \beta_s M/\rho_s$
5. Limiting apparent molar volume $\varphi_v = \varphi^0_v + S_v C^{1/2}$
6. Limiting apparent molar compressibility $\varphi_k = \varphi^0_k + S_k^{1/2}$
7. Intermolecular free length $L_f = K (\beta_s)^{1/2}$
8. Specific acoustic impendence $Z = \rho.u$

TableNo.1

Experimental Data of Density, Ultrasonic Velocity and Viscosity of Nifedipine Drug in Different Solvents at 300 K

Solvents	Conc.mol.dm^{-3}	Density ρ_sKgm^{-3}	Ultrasonic Velocity(u)m/s	Viscosityx10^{-3} Nsm^{-2}
40% Ethanol-Water Medium	0.02	928. 07	1543.7	1.1625
	0.03	928.28	1554.0	1.1632
	0.04	928.65	1576.7	1.1643
	0.05	928.79	1588.3	1.1655
	0.06	928.86	1595.9	1.1687
40% Acetone-Water Medium	0.02	1054.44	1649.3	1.2335
	0.03	1054.56	1661.2	1.2369
	0.04	1054.61	1675.6	1.2385
	0.05	1054.72	1681.9	1.2395
	0.06	1054.95	1689.7	1.2399
40% DMF-Water Medium	0.02	1012.41	1543.3	1.0531
	0.03	1012.52	1567.5	1.0543
	0.04	1012.73	1571.6	1.0556
	0.05	1012.84	1582.5	1.0567
	0.06	1012.96	1599.8	1.0586

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Table no.2
Variation of some acoustical parameters with concentration of Nifedipine Drug in different Solvents at 300K

Solvents	Conc.mol.dm^{-3}	β_s X 10^{-10} Pa^{-1}	Φ_v x10^{10} m^{3}mol^{-1}	Φ_k x10^8 m^{3}mol^{-1} Pa^{-1}	L_f X 10^{-11} (m)	Z x 10^5 Kg m^{-2} sec^{-1}
40% Ethanol - Water Medium	0.02	4.2611	4.96536	-50.8002	1.2448	15.2023
	0.03	4.2026	3.31020	-78.6983	1.2362	15.3109
	0.04	4.0805	2.48263	-103.195	1.2181	15.5431
	0.05	4.0181	1.98608	-121.5451	1.2087	15.6673
	0.06	3.9789	1.655051	-133.3359	1.2028	15.7483
40% Acetone-Water Medium	0.02	3.7330	4.96536	-199.967	1.1651	16.2423
	0.03	3.6782	3.310208	-216.0368	1.1565	16.3661
	0.04	3.6135	2.48263	-235.350	1.1463	16.5170
	0.05	3.5842	1.986085	-244.2635	1.1416	16.5885
	0.06	3.5494	1.65505	-254.877	1.1360	16.6739
40% DMF-Water Medium	0.02	4.2168	4.96536	-98.2474	1.2383	15.2821
	0.03	4.1794	3.31020	-8301099	1.2328	15.3533
	0.04	4.1705	2.48261	-77.7607	1.2314	15.3745
	0.05	4.1433	1.98608	-70.523	1.2274	15.4286
	0.06	4.1029	1.65505	-55.899	1.2214	15.5085

Table-3
Limiting values of ϕ^0_v and ϕ^0_k along with slope (S_v & S_k) for Nifedipine Drug in different medium at 300K temperature

Temp. T (K)	Medium	Parameters			
		ϕ^0_v x 10^{-5} m^{3}mol^{-1}	ϕ^0_k x 10^{-14} m^{3}mol^{-1}pa^{-1}	S_vx 10^{-5} m^{3}mol$^{-3/2}$dm$^{3/2}$	S_k x 10^{-14} m^{3}mol$^{-3/2}$dm$^{3/2}$pa^{-1}
300K	40% Ethanol -H_2O	-148.634	-77.65	473.88	326.95
	40% Acetone- H_2O	-76.643	-256.17	448.771	409.523
	40% DMF- H_2O	4.854	545.26	61.342	-1483.37

Table-4
A and β, coefficient values at 300 K in different medium for Nifedipine Drug

Medium	Coefficient	300K
40% Ethanol-Water medium	A	1.564
	β	-0.253
40% Acetone-Water medium	A	1.852
	β	-0.384
40% DMF-Water medium	A	0.453
	β	-0.118

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Results and discussion:

Table 1 shows that density (ρ), ultrasonic velocity (u) and viscosity (η) increases with increase in concentration for all three systems. The increase in ultrasonic velocity is due to decrease in intermolecular free length (L_f) as shown in table 2. This suggests that there is a strong interaction between Nifedipine drug and solvent molecule. Adiabatic compressibility (β_s) is a measure of intermolecular association or repulsion calculated from the measured ultrasonic velocity (u) and density (ρ). Adiabatic compressibility is found to decrease with increase in concentration. Since adiabatic compressibility is inversely related to the product of density and ultrasonic velocity based on this the compressibility is expected to decrease which has observed in the present case. When the sound waves travel through the solution, certain part of it travels through the medium and rest gets reflected by the ion i.e. restriction for flow of sound velocity by the ions. The character that determines the restriction movement of sound waves is known as acoustic impendence (Z). It has been found that acoustic impendence increases with increase in concentration. The apparent molar compressibility (φ_k) explains the solute-solvent and solute- solute interactions in solution and was calculated by using the equation no. (iv). The apparent molar volume (φ_v) is defined as the change in volume of solution for the added one mole of a particular component at constant temperature and pressure. It is thermodynamic property which helps in elucidating solvation behavior of electrolyte in solution. Apparent molar volume was evaluated from the density of solution and solvent.

It is evident from the table 3 that φ^0_k values are negative for 40% EtOH-water and 40% Acetone-water but for 40%DMF-water φ^0_k values are positive. The negative φ^0_k values are suggest solute- solvent interaction whereas positive values are due to solute- solute interaction, is further confirmed by φ^0_v values which are positive for 40% DMF-water and negative for 40%EtOH-water and 40% Acetone-water of the drug. Sv is a measure of solute – solvent interaction. It is observed from the table 3 that Sv values are higher in 40% EtOH-water and 40% Acetone-water and low in 40% DMF-water solution. This confirms that in 40% DMF-water solution solute- solute interactions and in 40% EtOH-water and 40% Acetone-water solute – solvent interaction predominates.

The viscosity β -Co-efficient has been derived from Jones-Dole equation

$$(c> 0.1m)\ \eta_r\text{-}1 / C^{1/2} = A+B\ C^{1/2}$$

Where $\frac{\eta}{\eta 0} = \eta_r$ is the relative viscosity A and β are the characteristics of the solute and solvent. A is Falkenhagen coefficient represent the contributor from solute-solute interaction and β is Jones Dole coefficient known to depend on the size of the solute particle and on the interaction between solute and solvent.

They were obtained by a least – squares treatment as intercept and slope of the linear plot of ηr-1 / $C^{1/2}$ Vs $C^{1/2}$. The graph for each system given linear straight-line showing validity of Jones-Dole equation. The slope of straight line gives value of β- co-efficient.

The viscosity A coefficient represent the ion-ion interactions and negative values have shown some physical significance. However negative 'A' values have also been reported to be in other solvents in some studies. The large and small value of 'A' shows the stronger and weaker solute – solute interactions respectively.

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When solute is introduced into solvent of organic-water mixture it will interfere with the ordered structure of water in the solute's co-sphere. As only one solute is present so such variation in the values of A can be explained.

In the present study viscosity of liquid solutions increases with increase in concentration of Nifedipine drugs solution in 40% ethanol-water, 40% acetone-water and 40% DMF-water mixture. The increase in viscosity with increase in concentration may be attributed to the increase in solute solvent interactions.

Viscosity β-coefficients have been established from ion- solvent interactions and are responsible for introducing order or disorder in the structure of the solvent. Solute with negative β-Coefficient is characterized as structure breakers indicating weak solute-solvent interactions. [18-23]

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Enhanced Gas Sensing Properties of Pd-incorporated Ce-$SmFeO_3$

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Abstract

This investigation deals with the incorporation of noble metal nanoparticles to Ce-$SmFeO_3$ sensing element for boosting its gas sensing performance. Series of Pd incorporated Ce-$SmFeO_3$ sensing elements Pd-CeSF1, Pd-CeSF2 and Pd-CeSF3 corresponding to dipping time 1 min, 2 min and 3 min, respectively, was prepared using simple dipping technique. Different dipping time interval ensures the incorporation of different concentrations of Pd on the surface of Ce-$SmFeO_3$. Porous microstructures of all the samples were observed in FE-SEM images. Incorporation of Pd and variation in the concentration of Pd were seen in elemental analysis. Ethanol gas response of Pd-CeSF1, Pd-CeSF2 and Pd-CeSF3 were measured. For 60 ppm ethanol gas, response of Pd-CeSF1 increased to 37.2 which was about 2.2 times more than the previously recorded response of 16.87 for CeSF. Additionally, shift in the corresponding optimal operating temperature from 100^0C to 80^0C was also observed. The contribution of palladium nanoparticles in increasing response of Pd-CeSF1towards ethanol gas and decaying its optimal operating temperature was elaborately discussed.

Keywords: Pd incorporated Ce-$SmFeO_3$, Noble metal, Ethanol sensor, Catalyst, Perovskite.[1]

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1. Introduction

Detection of target gas by semiconductor metal oxide based gas sensor is governed by the adsorption of gas molecules on the oxide surface of sensor [1]. The performance of chemiresistive gas sensor is influenced by the availability of adsorption sites. The availability of adsorption sites can be enhanced by increasing surface area. More adsorption sites are available if surface area is large. Preparation of SMOs with different morphologies is a general approach to increase the surface area [2]. Beside this, doping of base material has been frequently reported to increase the sensitivity of SMO [3-5]. Doping with noble metals seems to be more effective owing to their high catalytic activities [6-7]. Nobel metals can incorporate additional active surface sites thereby improving the adsorption of target gases.

P-type semiconducting $SmFeO_3$ is well known for its ability to detect ozone, NO_2 which are oxidizing gases [8-10]. Extremely low electrical conductivity and reducibility make $SmFeo_3$ unsuitable for monitoring VOCs and reducing gases [11]. But modified $SmFeO_3$, permitted due to its perovskite structure, has potential to sense even reducing gases like ethanol. Gas sensing properties of Co doped $SmFeO_3$ have been reported by some authors [12-14]. Ethanol, a well known volatile organic compound, has its present in foods, chemical industries etc [15]. Because of its toxicity, ethanol can cause liver damage, skin irritation etc. and therefore its monitoring has become essential. Doped semiconductor metal oxides and perovskite-type oxides based gas sensors have been fabricated by some researchers for monitoring of ethanol [16-18]. Although these sensors can detect ethanol, its gas response and optimal operating temperature has to be enhanced.

Previously, we have also prepared a series of Ce surface modified $SmFeO_3$ films by changing the dipping time intervals (1 min, 3 min and 5 min) and observed that all the films were selective to ethanol gas. The film having dipping time 5 min has maximum ethanol gas response (16.87) at optimal operating temperature 200^0C. With the literature review that noble metal incorporation boosted the gas sensing performance; in present work we incorporated Pd in various concentrations to this best Ce modified $SmFeO_3$ film and investigated the impact of Pd on its ethanol gas sensing characteristics.

2. Experimental

Our earlier publications demonstrated the fabrication of Ce modified $SmFeO_3$ sensor elements in the form of thick films [19]. In present work we used Ce modified $SmFeO_3$ film with dipping time of 5 min and marked it as CeSF. For incorporating Pd noble metal to CeSF, palladium (II) nitrate solution was taken. To this solution, CeSF films were dipped for different time intervals. Films with dipping timing 1 min, 2 min and 3 min were marked as Pd-CeSF1, Pd-CeSF2 and Pd-CeSF3 respectively. All the films were dried in air, fired in Muffle furnace and then treated for further investigations.

As prepared Pd-CeSF samples were investigated by FE-SEM and EDX methods. With FE-SEM, morphology of samples was visualized and with EDX, the concentration and dispersion of Pd was depicted. Gas sensing characteristics of samples were studied in static gas sensing set-up under 60 ppm ethanol gas. The resistance values of sensors

were R_g and R_a respectively in presence of ethanol and air. Gas response is then calculated as(R_g/R_a) [20].

3. Results and Discussion

3.1. Characterization of Pd -CeSF

X-ray spectrum of $SmFeO_3$ powder was investigated in our earlier publication which confirmed the formation of single phase perovskite oxide with orthorhombic symmetry [14].

FE-SEM images of Pd-CeSF1, Pd-CeSF2 and Pd-CeSF3 were shown in Figure 1.

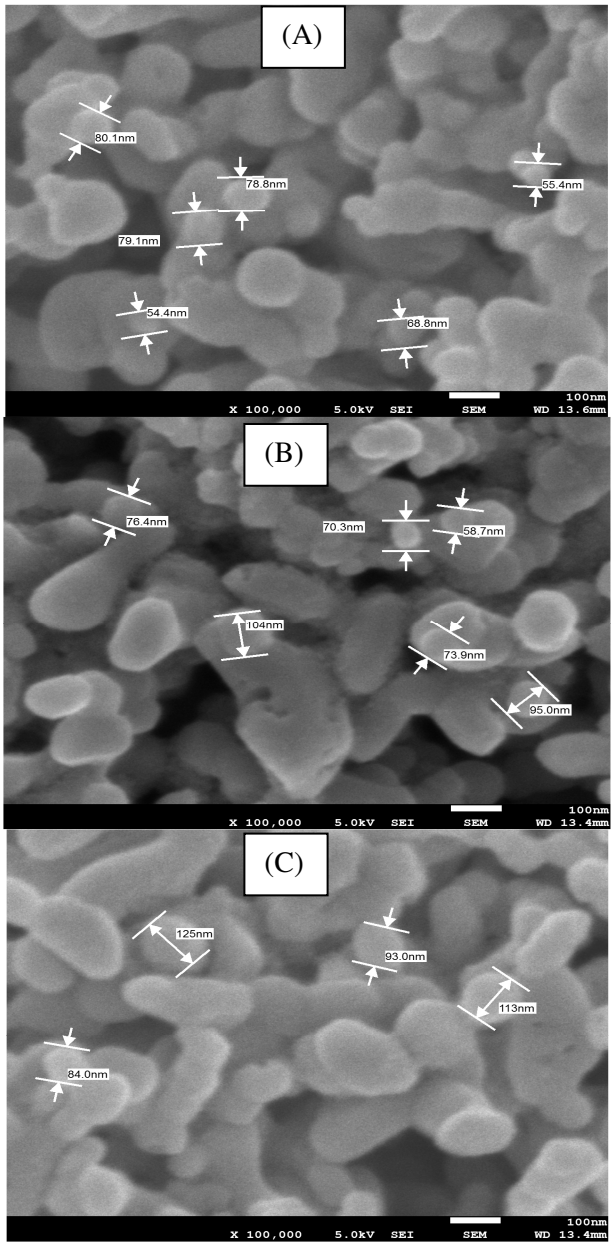


Figure 1. FE-SEM images of (A) Pd-CeSF1, (B) Pd-CeSF2 and (C) Pd-CeSF3

All the films seem to be consists of number of nanoparticles distributed non-uniformly and/or the cluster of nanoparticles at the surface. The average particle size ranges from 54 nm to 84 nm. The smallest average particle size (54.4 nm) was recorded in Figure 1(A) which is FE-SEM image of Pd-CeSF1 with dipping time 1 min. High porosity was observed on the surface of all the samples as compared to porosity of CeSF sample presented in earlier publication [19]. Pd-CeSF1film appears to have high porosity among Pd incorporated CeSF films.

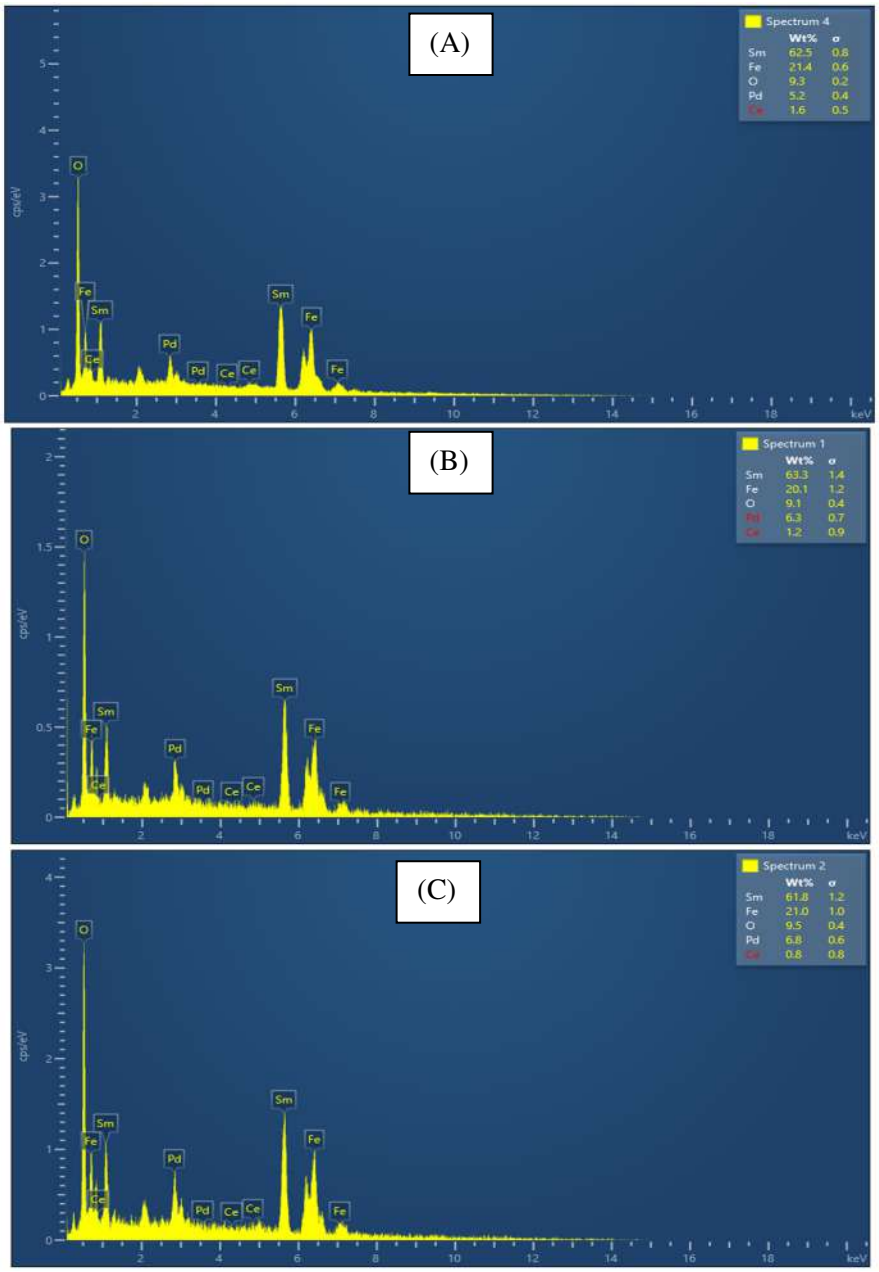


Figure 2. EDX spectra of (A) Pd-CeSF1, (B) Pd-CeSF2 and C) Pd-CeSF3

The EDX spectrum of Pd-CeSF1, Pd-CeSF2 and Pd-CeSF3 are shown in Figure 2. The results provide the confirmation of successful incorporation of Pd to CeSF film. Additionally concentration of incorporated Pd was found to be increased with the increase in dipping time.

3.2. Ethanol-sensing characteristics of Pd-CeSF

In order to determine optimal operating temperature, ethanol gas response of Pd-CeSF1, Pd-CeSF2 and Pd-CeSF3 based sensors were measured, by changing the operating temperature from 30 ^{0}C to 350 ^{0}C, towards 60 ppm ethanol gas concentration. The observations demonstrated that the optimal operating temperatures for Pd-CeSF1based sensor was 80 ^{0}C, and that for Pd-CeSF2 and Pd-CeSF3 based sensors was 100 ^{0}C. Figure 3 represents response of CeSF and Pd-CeSF films to 60 ppm ethanol in the operating temperature range 30^{0}C to 350^{0}C.

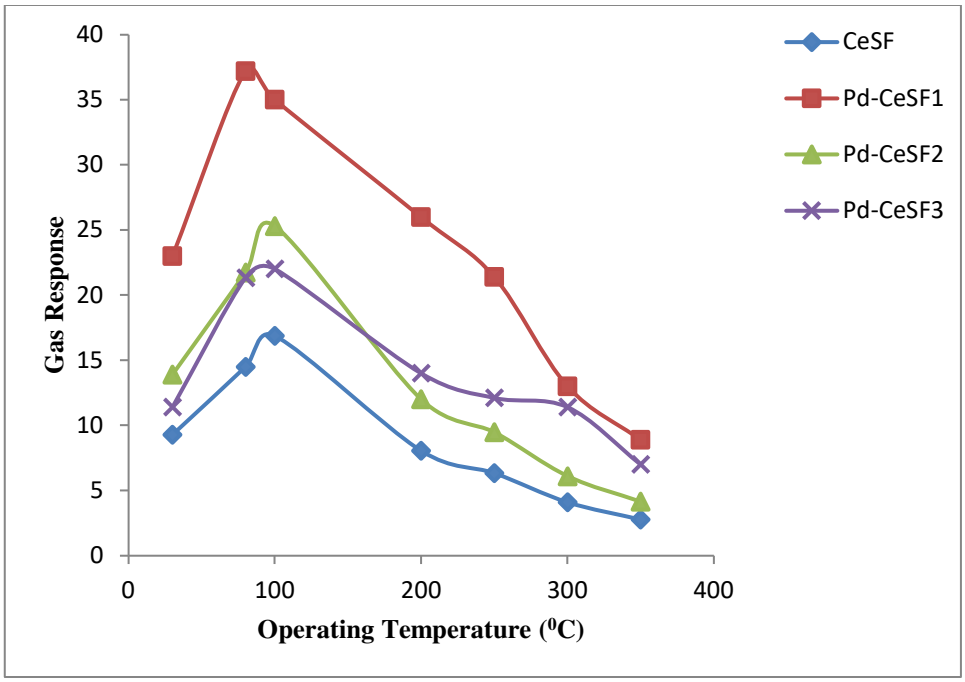


Figure 3. Response of CeSF and Pd-CeSF Films to 60 ppm Ethanol

The graph shows that all the three samples exhibited similar behavior in gas response and operating temperature. With the increase in operating temperature, growth in gas response was observed initially which then tended to decay in gas response with further increase in operating temperature. The carrier concentration and the activation energy of surface reactions strongly affect the values of gas response of sensor. The operating temperature of sensor has direct correlation with these two factors. The initial increase in gas response with operating temperature may be the result of activation of gas molecules and the trapping of conduction electrons [21]. The decay in gas response with further increase in operating temperature may be due to the fall in adsorption rate

than desorption rate. For samples Pd-CeSF1, Pd-CeSF2 and Pd-CeSF3, the maximum values of gas response were 37.2, 25.3 and 22 which were obtained at corresponding optimal operating temperatures 80^0C, 100^0C and 100^0C respectively. The results indicate that Pd doping improved the gas response and also decreased the optimal operating temperature.

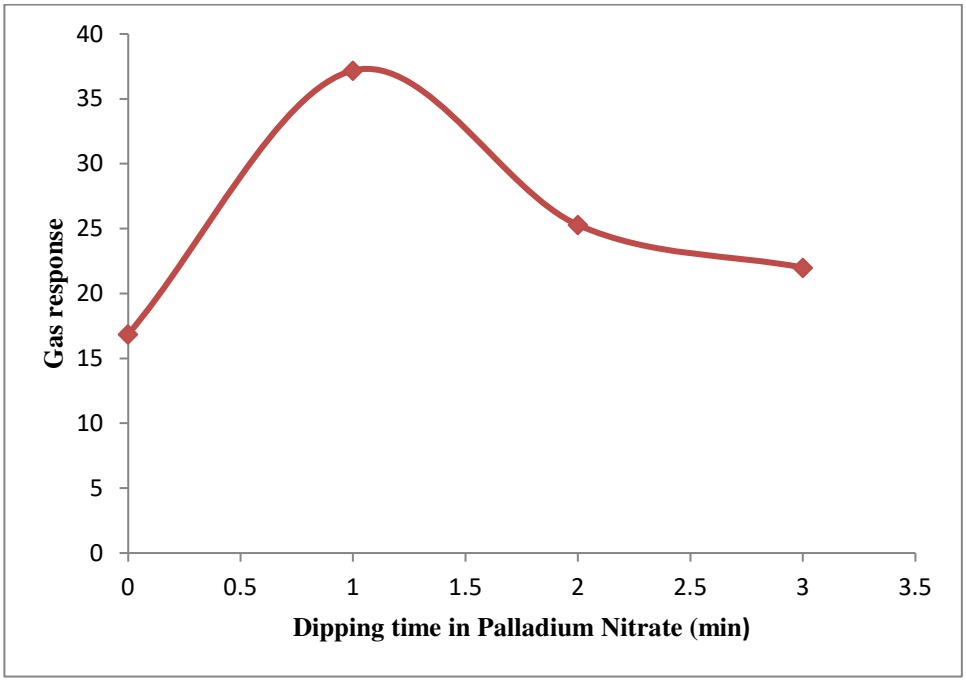


Figure 4. Ethanol Gas Response Variation with Dipping Time

Pd doping enhances the gas response but only optimum concentration of Pd can present maximum ethanol gas response. Increasing and then decreasing behavior of ethanol gas response with Pd concentration (or dipping time) was observed here as depicted in Figure 4.The surface defects increase with Pd concentration but not always. Concentration of Pd corresponding to dipping time 1 min was sufficient to produce maximum ethanol gas response. At this Pd concentration, best catalytic and sensitization effect of Pd could be observed. But at comparatively high Pd concentration (dipping time 2 min and 3 min), aggregation of Pd nanoparticles decreased the active sites and hence gas response was decreased.

To examine the stability of sensor, its response was noted regularly for 60 days. During this period, sensor showed almost constant gas response as shown in Figure 5.

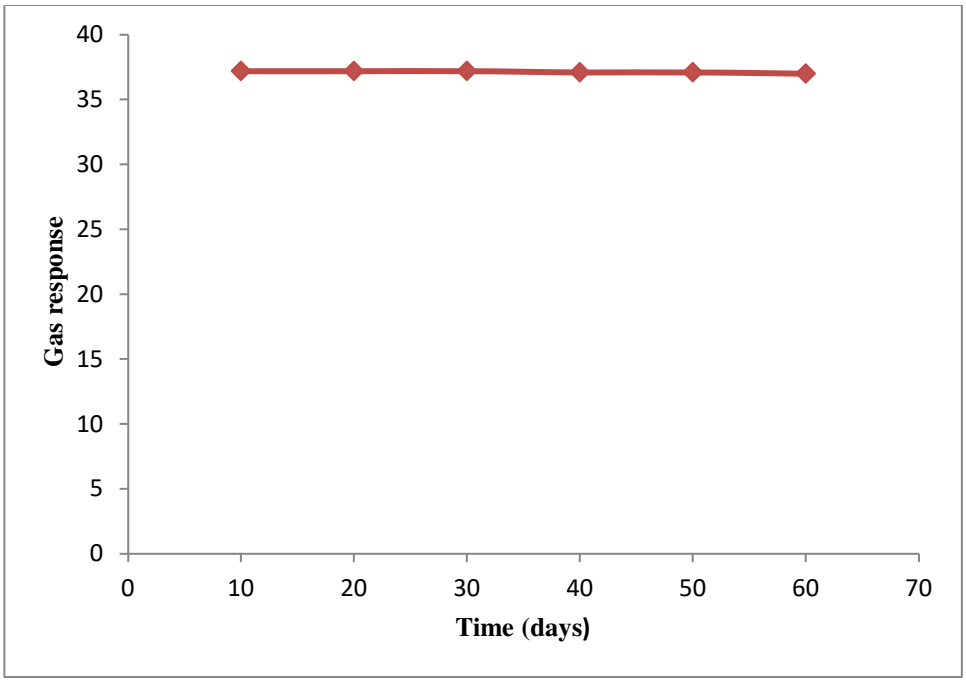


Figure 5. Stability of Pd-CeSF1-based Sensor

3.3. Ethanol-sensing mechanism of Pd-CeSF

According to ethanol gas sensing mechanism frequently reported by many authors, in ambient air, chemisorption of oxygen gas occurs on the surface of sensor [21]. This chemisorption includes i) adsorption of oxygen molecules from air and ii) absorption of electrons in the material by these adsorbed oxygen molecules to decomposed into molecular or ionic species depending on the temperature. The formation of electron hole accumulation layer near the surface is the final result of chemisorption of oxygen molecules which decreases the sensor resistance. When ethanol gas enters into the chamber, it is also adsorbed on the surface. The adsorbed ethanol gas reacts with chemisorbed oxygen ions to produce H_2O and CO_2 gases followed by reverting of captured electrons to the material. This so called desorption process reduces the width of hole accumulation layer resulting in the increase of sensor resistance.

When Pd is incorporated into CeSF sensor, the activation energy of surface reactions is decreased because of the reaction paths provided by Pd. Further, additional active surface sites are produced that boost the adsorption of ethanol gas. For palladium noble metal, chemical sensitization and electronic sensitization were reported to be impacting factors for boosting gas sensing performance [22-23]. Among them, chemical sensitization arises due to spill-over effect. The Pd nanoparticles now serve as active sites for adsorption and dissociation of oxygen molecules in ambient air. In ethanol gas environment, gas molecules are dissociated into corresponding atoms through catalytic activity of Pd. Then these dissociated atoms spill over from noble metal to the surface of metal oxide. Thus the rate of surface reactions is improved due to subsequent spillover. On the other hand, electronic sensitization originates due to the different fermi levels of SMO and Pd nano material. Pd nanoparticles also absorb electrons from SMO and the potential barrier is elevated [24].

4. Conclusion

Palladium nanoparticles were incorporated to Ce modified $SmFeO_3$ films (dipping time 5 min). As-prepared Pd-CeSF1, Pd-CeSF2 and Pd-CeSF3 films exhibited enhanced response to 60 ppm ethanol. In particular, Pd-CeSF1based sensor has maximum response (37.2) at lower operating temperature 80^0C. The enhanced ethanol gas sensing characteristics of Pd decorated Ce modified $SmFeO_3$ films were the results of sensitization mechanism of palladium.

Acknowledgment

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Characterization of Co-surface modified nanocrystalline $SmFeO_3$ thick film

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Abstract

Samarium orthoferrite $SmFeO_3$ thick films prepared by screen printing technique were surface modified with cobalt chloride. Surface modification was achieved by dipping technique. $SmFeO_3$ thick films were dipped into 0.1 M aqueous solution of cobalt chloride for 5 min. After drying, the modified films were fired in Muffle furnace at 550^0C for 30 min. $SmFeO_3$ powder was analyzed by X-ray diffraction (XRD) and Fourier Transform Infrared spectroscopy techniques. The observations depict that powder sample is made up of $SmFeO_3$ nanoparticles. As-fabricated pure and Co-surface modified $SmFeO_3$ thick films were analyzed by Field Emission Scanning Electron Microscope (FE-SEM) to observe its microstructure. The FE-SEM results revealed the formation of nanocrystalline $SmFeO_3$ grains and the porosity of films. For the conformation of Co deposition, the Energy-dispersive X-ray (EDAX) analysis of the Co modified $SmFeO_3$ thick film was carried out. The EDAX analysis showed that Co was successfully deposited on pure $SmFeO_3$ surface with no additional impurities. The effect of Co modification on the surface morphology of pure $SmFeO_3$ thick film was discussed.

Keywords: Surface modification, Orthoferrite, Dipping method, FE-SEM, Nanocrystalline, $SmFeO_3$.

1. Introduction

Scientists have shown great interest in examining the properties of nanostructured semiconductor metal oxides. Various semiconductor metal oxides and their composites have been continuously investigated for different applications. The physical and chemical properties of metal oxides are related to the morphology of material. Methods of synthesis, nature of dopant, concentration of dopant, and annealing temperature have been reported to influence the morphology of material.

Perovskite-type oxides with general formula ABO_3 (A=rare earth and B= transition metals) have shown excellent tunable physical and chemical properties. Among them, rare earth orthoferrites have been employed in various fields including solid state gas sensors [1-3]. Rare earth orthoferrite has orthorhombic distorted structure in which Fe ions prefer central position whereas rare earth ions prefer non-central position [3]. Some of the ABO_3 type rare earth orthoferrites such as $LaFeO_3$ and $SmFeO_3$ have been reported for the detection of oxidizing and reducing gases [4-7]. Particularly, $SmFeO_3$ which belongs to Pbnm space group (#62), exhibited p-type electrical conductivity, oxygen-ion mobility and high catalytic activity towards oxidizing gases [8-10]. Therefore, $SmFeO_3$ can be considered as good sensing material for the detection of oxidizing gases. But $SmFeO_3$ based gas sensors generally operate at high operating temperature because the electrical conductivity of $SmFeO_3$ is extremely small at lower temperature. Further, problem of stability at high temperature in reducing environment arises for $SmFeO_3$. In perovskite structure, nature of A-site and B-site ions controls the electrical conductivity and the stability of material. Therefore, modified $SmFeO_3$ can have enhanced electrical conductivity and stability. Literature survey reveals that $SmFeO_3$ can be modified with Co, Ce, Ni and Mg. S. M. Bukhari et al. examined the effect of Ce doping on $SmFeO_3$ and concluded that Ce-doped $SmFeO_3$ enhanced electrical conductivity as well as stability [11]. H. Zhang et al. prepared $SmFe_{0.9}Mg_{0.1}O_3$ by sol gel method and obtained excellent response towards 0.5 ppm acetone vapour [12]. Mir et al. reported that Ni doping in nanostructured $SmFeO_3$ results in an increase in porosity and decrease in optical band gap energy [13]. Ma Zhao et al. illustrated influence of Co-doping in structural and electrical properties of $SmFeO_3$ nanostructure thereby suggesting that $SmFe_{0.7}Co_{0.3}O_3$ was good material for ethanol sensor [9].But, Co-O bond is weaker than Fe-O bond. Therefore researchers suggested the controlled addition of Co to pure $SmFeO_3$ for increasing electrical conductivity.

Thus, from the literature survey on $SmFeO_3$ it is clear that the physico-chemical properties of are associated with grain size and surface morphology. For this reason, synthesis of doped $SmFeO_3$ nanomaterials of well defined morphology has become an area of interest. Sol-gel method, co-precipitation method, hydrothermal method etc have been frequently used for the synthesis of $SmFeO_3$ nanoparticles. For the addition of dopants to pure material, doping technique and dipping technique are regularly employed. Doping technique involves the addition of dopants in desired proportion at the time of synthesis of material. On the other hand, with dipping technique, additives can be deposited on the surface of pristine material. Modification of $SmFeO_3$ by doping technique was adopted by most of the researchers.

In present work, an attempt has been made to modify screen printed nanocrystalline $SmFeO_3$ thick film with Co by dipping technique. As-prepared Co-surface modified $SmFeO_3$ thick films are characterized by different characterization techniques.

2. Experimental

Preparation of nanocrystalline $SmFeO_3$ powder by sol-gel method was described in earlier publications [14]. The procedure includes mixing of stoichiometric amounts of samarium nitrate, iron nitrate and citric acid monohydrate (in the proportion 1:1:1). The mixture was grounded into Agate mortar for 30 min. Ethylene glycol was added to the mixture provided with constant stirring at 75^0C for 2 h. The sole was then dried into gel which was finally calcinated in Muffle furnace at 800^0C for 4 h to obtain powder sample.

The formulation of thixotropic paste of $SmFeO_3$ powder follow the procedure described elsewhere [15-17]. The paste was screen printed on the glass substrate to obtained pure $SmFeO_3$ thick films. These films are allowed to dry and then fired in Muffle furnace for 30 min at 550^0C.

For surface modification, 0.1 M aqueous cobalt chloride solution was taken in Petri dish to which $SmFeO_3$ films are dipped for 5 min. After natural drying, Co-modified $SmFeO_3$ thick films were again fired for 30 min at 550^0C. The films so prepared are named as "Co-surface modified $SmFeO_3$ thick film".

EXPERT-PRO PW 3071 powder diffractometer was used to obtain X-Ray Diffraction (XRD) pattern of pure $SmFeO_3$ powder. To obtain the information about the functional groups and the vibrational modes present in the system, Fourier Transform Infrared (FTIR) spectrum of $SmFeO_3$ powder was recorded on Shimadzu NIR spectrophotometer in the range of 400-4000 cm^{-1}.

The morphological and the elemental analysis of the films were carried out by Field Emission Scanning Electron Microscope (FE-SEM) coupled with Energy Dispersive X-ray Spectrometer (EDAX) (JSM- 7610F, JEOL Japan operated at 15 kV).

3. Results and Discussion

3.1 XRD analysis

XRD pattern of pure $SmFeO_3$ powder prepared by sol-gel method is already presented in earlier publication [10]. The results confirmed that $SmFeO_3$ powder has orthorhombic structure and Pnma space group. Applying Debye Scherrer's formula, the average crystallite size was calculated as 50.08 nm.

3.2 FTIR analysis

Fig. 1 depicts FTIR spectrum of pure $SmFeO_3$ powder sample. Two prominent absorption peaks are seen at 554 cm^{-1} and 411 cm^{-1} which confirms the formation of $SmFeO_3$ crystal structure (orthorhombic perovskite). Peak obtained at 554 cm^{-1} is ascribed to Fe-O stretching mode of vibration. Another peak obtained at 411 cm^{-1} corresponds to O-Fe-O bending mode of vibration. The absorption peaks around 2931 cm^{-1} corresponds to C-H vibration mode. Band around 1112 cm^{-1} is ascribed to C-O bond. On exposure to ambient atmosphere, carbonate species are adsorbed on the surface and results in above bands.

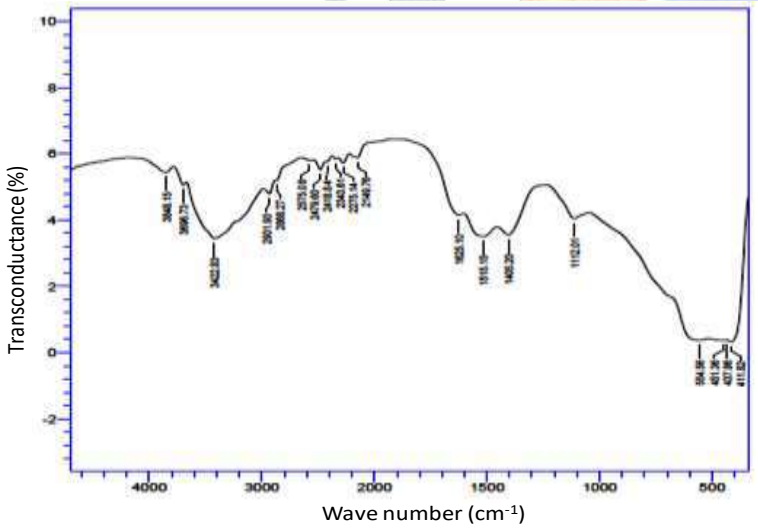


Fig. 1: FTIR spectrum of pure $SmFeO_3$ powder.

3.3 FE-SEM analysis

To analyze the microstructure of Co-modified $SmFeO_3$ thick film, field emission scanning electron microscope was used. The FE-SEM image of Co-surface modified $SmFeO_3$ thick film is shown in Fig. 2.

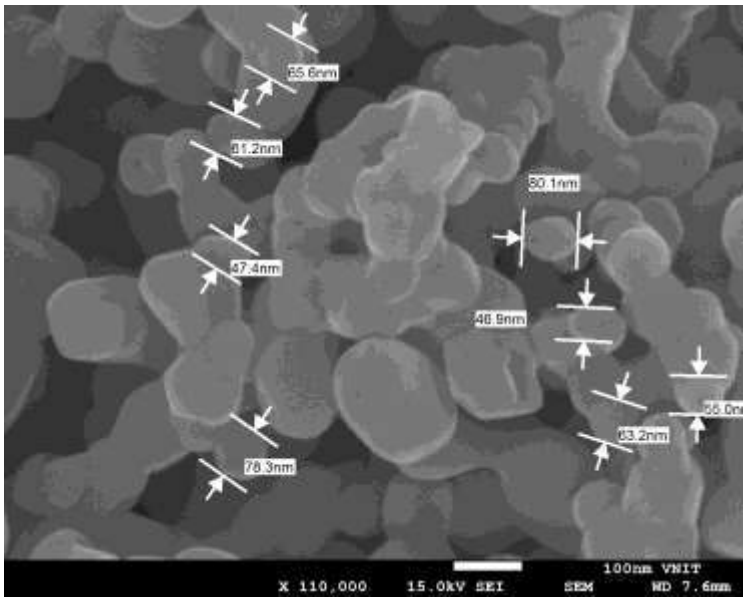


Fig. 2: FE-SEM image of Co-surface modified $SmFeO_3$ thick film (dipping time 5 min).

Crystalline, nanostructured $SmFeO_3$ particles are observed on the surface of film. The particle size ranges from 47 nm to 80 nm. Particles are irregular in shape and distributed non-uniformly. The spherical morphology is observed for some particles and the agglomerations of some fine particles are also observed. A careful observation of micrograph depicts that some smaller particles are distributed around larger grains. These smaller particles may be Co species and can be confirmed from elemental analysis. The micrograph depicts that the average particle size for $SmFeO_3$ is 62 nm which is less than the average particle size (84 nm) observed for undoped $SmFeO_3$. Thus, Co doping has reduced the particle size which is consistent with the observations reported in other works [9]. Particle size is considered to be an important parameter affecting the sensitivity of sensor. Smaller size of nanoparticles tends to increase the sensitivity of sensor. The surface of film seems to be smooth and porous due to the presence of large numbers of $SmFeO_3$ grains. Therefore Co-surface modified $SmFeO_3$ thick film may favor the adsorption and desorption processes in gas sensing mechanism.

3.4 EDAX analysis

Using energy dispersive X-ray spectrometer, elemental compositions of Co-surface modified $SmFeO_3$ thick film are determined. Fig. 3 shows the EDAX spectrum for Co-surface modified $SmFeO_3$ thick film. The sharp peaks observed in EDAX spectrum confirm the presence of Sm, Fe, O and Co on the film. No other peak is observed in the spectrum indicating the purity of sample. From EDAX spectrum, wt% of Sm, Fe, O and Co are observed and presented in table 1.

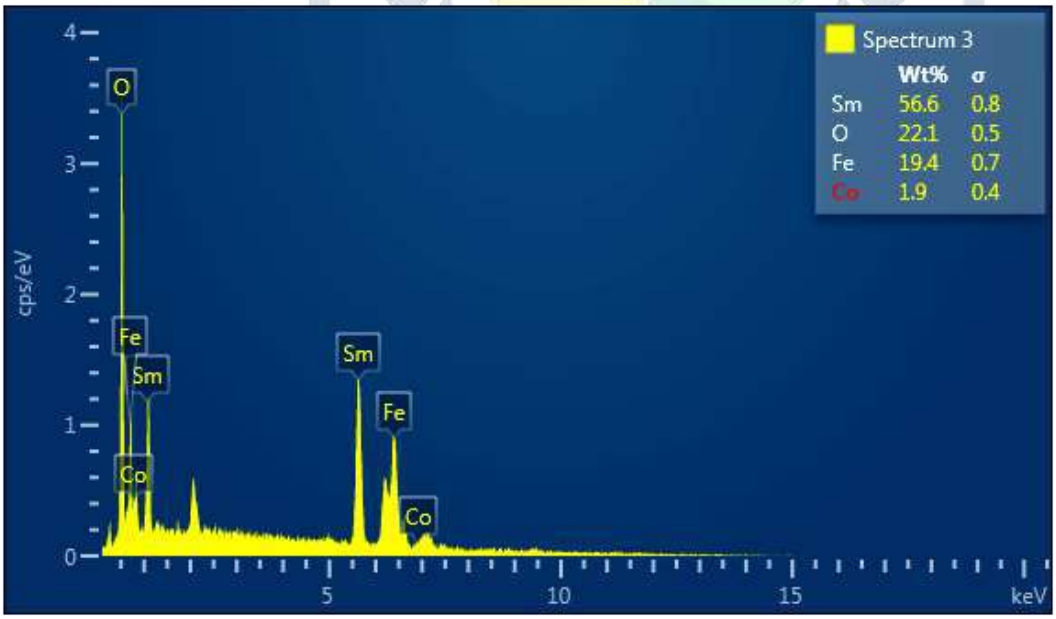


Fig. 3: EDAX spectrum of Co-surface modified $SmFeO_3$ thick film (dipping time 5 min).

Table 1: Elemental composition of Co-surface modified $SmFeO_3$ thick film (dipping time 5 min)

Sample	Elemental composition (wt%)			
	Sm	Fe	O	Co
Co-modified $SmFeO_3$	56.6	19.4	22.1	1.9

Co may have replaced Sm or Fe or both in perovskite structure of $SmFeO_3$ during surface modification. For 5 min dipping time, concentration of Co deposited on the surface of pure is 1.9 wt%

4. Conclusions

Co-surface modified $SmFeO_3$ thick films are successfully prepared by simple dipping technique. As prepared Co- surface modified $SmFeO_3$ thick film has crystalline microstructure and porous surface. Average grain size is reduced from 84 nm to 64 nm due to Co surface modification. Deposition of Co species on $SmFeO_3$ surface is confirmed from EDAX spectrum.

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Preparation of Zinc doped Magnesium Ferrite Nanoparticles by Sol-Gel Method

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1. Introduction

During the last decade, the world has seen huge interest in developing and understanding the matter of nanometric scale. It has allowed the scientists to develop and characterize materials with prominent properties and nanometric sizes. Due to the note-worthy properties, exhibited by nonmaterial, they have become centre of attention in the scientific community. The fabrication of spinel-structured ferrite nanoparticles has been intensively investigated in recent years due to their unique physical and chemical properties, as well as technological applications in ferrofluids [1], high-density magnetic recording media [2], biomedicine [3] and radar-absorbent materials [4].

Spinel ferrites, MFe_2O_4 (M = Mg, Mn, Fe, Co, Ni, Zn, Cu, Cd, etc.) are a technologically important group of materials. Among different ferrites, magnesium ferrite ($MgFe_2O_4$) enjoys a special attention because of its vast applications in high density recording media, heterogeneous catalysis, adsorption, sensors and magnetic technologies. $MgFe_2O_4$ is a partially inverse spinel and its degree of inversion is sensitive to the thermal history of the sample, microstructure and preparative parameters. Nanoparticles of $MgFe_2O_4$ have good photo electrical properties [5-7]. To fabricate various types of nanoparticles, a large number of methods are used such as physical, chemical, biological and hybrid methods. The nanoparticles synthesized using each method exhibit particular properties. So, the synthesis of nanostructured materials has become a particularly important area of research.

There are several methods for synthesizing nanosized spinel ferrite particles such as hydrothermal, co-precipitation, combustion, sol–gel, precursor, spray drying and freeze drying, microemulsion and reverse micelle method [8–15]. To prepare nanoferrites with simple routes by using cheap, non-toxic and eco-friendly precursors are still the core issue, among other proven synthesis methods [16]. Among these methods, the nanoparticles prepared by sol-gel method have been studied, although this synthesis provides a quick and easy way to prepare nanoparticle, it usually produces sample with large size distribution and less defined crystal chemistry.

ISSN 2454-1974

Herein, the purpose of this work is to prepare nanocrystalline Zn doped Mg spinel ferrite by a sol-gel method with a low calcination temperature involving low cost metal nitrates as raw materials and study of their structural properties.

2. Experimental

Preparation of nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$ powder was synthesized by the sol-gel technique. All chemicals were of analytical grade and were used without further purification. The stoichiometric molar amounts of Ferric nitrate [$Fe(NO_3)_3.9H_2O$], Magnesium nitrate [$Mg(NO_3)_2.6H_2O$], Zinc nitrate [$Zn(NO_3)_2.6H_2O$] and Citric acid [$C_6H_8O_7.H_2O$] were weighed separately with a ratio 0.5M:0.25M:0.5M. These reagents were mixed with distilled water and volume made up to 100 ml. The solution mixture was stirred and heated at 60°C for 3 h and followed by 80°C, until the mixture changed to gel form. The gel was then dried in an oven at 100°C for 24 h. The obtained powder was then calcined in a muffle furnace at 700°C for 2 h to improve the crystallinity of the prepared material. Finally, brown color powder was obtained. Taken solid phase sample was grinded in a mortar to make it powder for further analysis.

The phase confirmation was determined using XRD (Bruker, AXD D8-Discover using Cu Kα radiation with an accelerating voltage 40 kV). FT-IR image was recorded using 3000 Hyperion Microscope with Vertex 80 (Bruker, Germany) to provide information about the structural coordination in the powder sample. The TEM image was recorded using CM 200 (Philips) with an accelerating voltage of 20-200 kV.

Appropriate quantity of mixture of organic solvents such as butyl cellulose, butyl carbitol acetate and turpineol was added to the mixture of $Mg_{0.5}Zn_{0.5}Fe_2O_4$ and a solution of ethyl cellulose (a temporary binder). The mixture was then ground to form paste. The paste obtained was screen printed onto a glass substrate in desired patterns. The thick films so prepared were fired at 500°C for 1 h. Surface morphology of thick film was observed by using SEM (JSM-7600F microscope) with an accelerating voltage of 0.1 to 30 kV.

3. Result and discussions

3.1 XRD analysis

The X-ray diffraction pattern of $Mg_{0.5}Zn_{0.5}Fe_2O_4$ calcinated at 700°C for 2 h was exhibited in Fig. 1. Main peaks were found at 2θ values = 29.90°, 35.21°, 56.58°, 62.14° and 73.48° which were identified as corresponding to Miller index (220), (311), (400), (511) and (440) respectively (JCPDS card no. 73-2211). The XRD peaks and their positions with the calculated lattice parameter confirm that all the compositions exhibit single-phase cubic spinel structure with Fd3m space group. No peaks from other phases are detected, indicating high purity of the products.

The average crystallite size (D) was calculated from XRD peaks broadening using the Debye-Scherrer approximation, which is defined as

ISSN 2454-1974

$$D = \frac{K\lambda}{\beta\cos\theta} \quad (1)$$

where, D is the average crystallite size, k is a constant equal to 0.9, λ is the X-ray wavelength and β is the peak full width at half maximum (FWHM) and θ is the angle of diffraction.

However, the lattice constant of as-synthesized ferrite powder was a= 8.421A°. A similar linear variation of lattice constant with Zn content has been observed by El-Sayed [17] and Kakatkar et al. [18] for M–Zn ferrites with M = Ni, Co, Cu, Mg. The average crystallite size was determined from the XRD powder pattern using Debye–Scherrer formula and was found to be 30 nm.

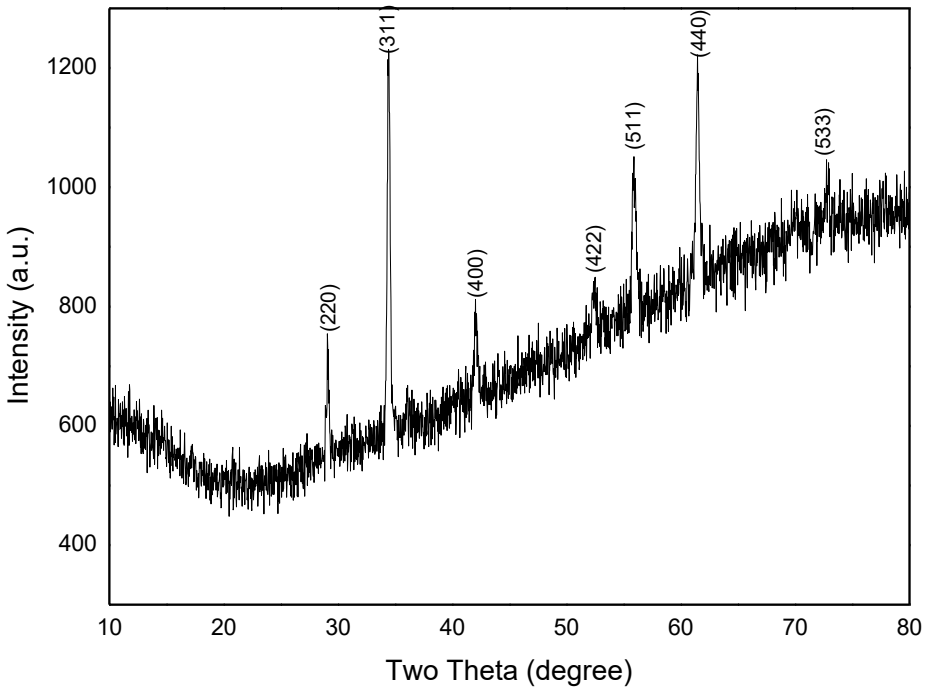


Fig. 1. XRD pattern of $Mg_{0.5}Zn_{0.5}Fe_2O_4$ calcined at 700°C.

3.2 FT-IR analysis

FT-IR spectrum of $Mg_{0.5}Zn_{0.5}Fe_2O_4$ nanoparticle was presented in Fig. 2. Vibrations of ions in the crystal lattice were usually observed in the range of 4000 - 400 cm^{-1} in IR analysis. Two main broad metal-oxygen bands were seen in the IR spectra relative to spinel ferrite compounds. Infrared spectrum shown in Fig. 2 had two absorption bands near about 400 cm^{-1} and 600 cm^{-1} for octahedral and tetrahedral sites

ISSN 2454-1974

respectively. Waldron [19] attributed the higher absorption band position (600 cm^{-1}) to the intrinsic stretching vibrations of tetrahedral complexes and the lower absorption band position (400 cm^{-1}) to octahedral-metal stretching because of the difference in Fe^{3+}– O^{2-} distances for the octahedral and tetrahedral sites respectively. The Mg^{2+} ions occupy mainly the octahedral sites but fraction of these ions may be migrated into tetrahedral sites. This would explain the existence of a weak shoulder in the range of 690 –710 cm^{-1}. This confirms that the Mg ferrite has a partially inverse spinel structure.

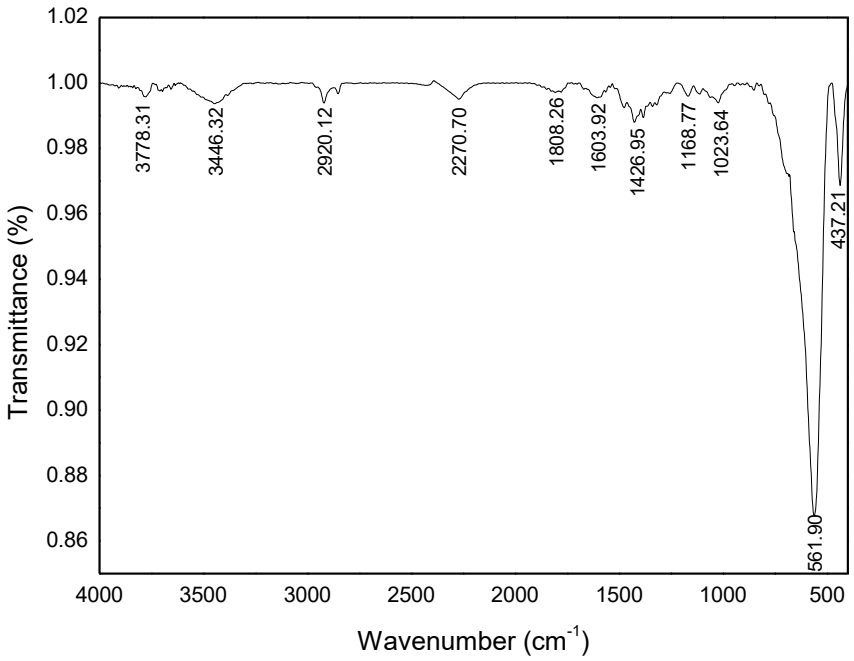


Fig. 2. FTIR spectrum of nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$.

3.3 TEM analysis

The size and morphology of the obtained $Mg_{0.5}Zn_{0.5}Fe_2O_4$ nanocrystal was characterized by TEM observation. Fig. 3(a) shows TEM image of $Mg_{0.5}Zn_{0.5}Fe_2O_4$ nanoparticle. The corresponding SAED pattern is shown in Fig. 3(b). As can be seen from Fig. 3(a) and (b), the prepared product consists of small sized nanocrystals with irregular shapes. It appears that a higher temperature reaction favors a particle with larger grain sizes, because a higher temperature enhanced the atomic mobility and caused the grain growth to result in a better crystallinity. As it can be seen that the result estimated from TEM micrograph was in good accordance with the XRD

ISSN 2454-1974

analysis. The selected area aperture used in this study sufficed to reveal all the corresponding bright rings of the spinel structure. It was observed that the spot type pattern which is indicative of the presence of single crystallite particles and no evidence was found for more than one pattern, suggesting the singlephase nature of the material.

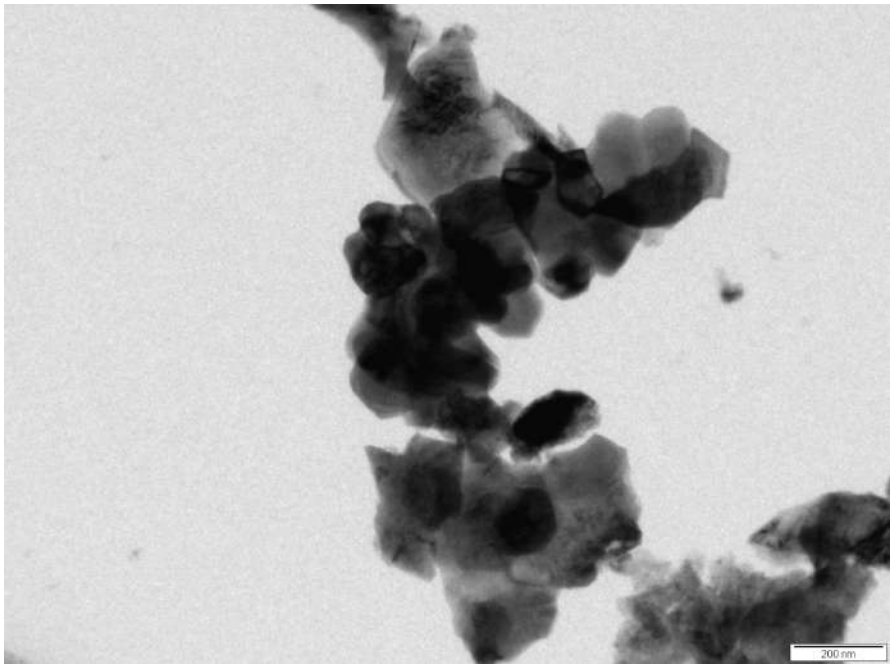


Fig. 3(a). TEM image of nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$.

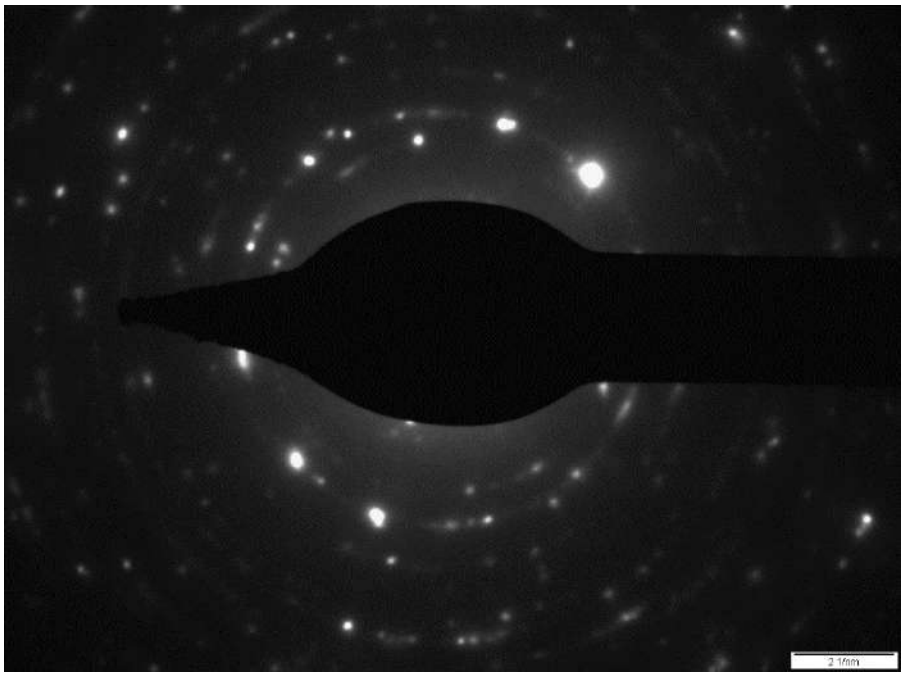


Fig. 3(b). SAED micrograph of nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$.

ISSN 2454-1974

3.4 SEM analysis

SEM technique was employed for finding morphology of the thick film. Fig. 4 shows SEM image of the nanocrystalline spinel $Mg_{0.5}Zn_{0.5}Fe_2O_4$. The SEM technique was employed for finding morphology of the powder; it shows formation of the agglomerated particle. SEM image shows that the sample exhibit large grains structure having irregular morphology (polygons) with the presence of soft agglomerations.

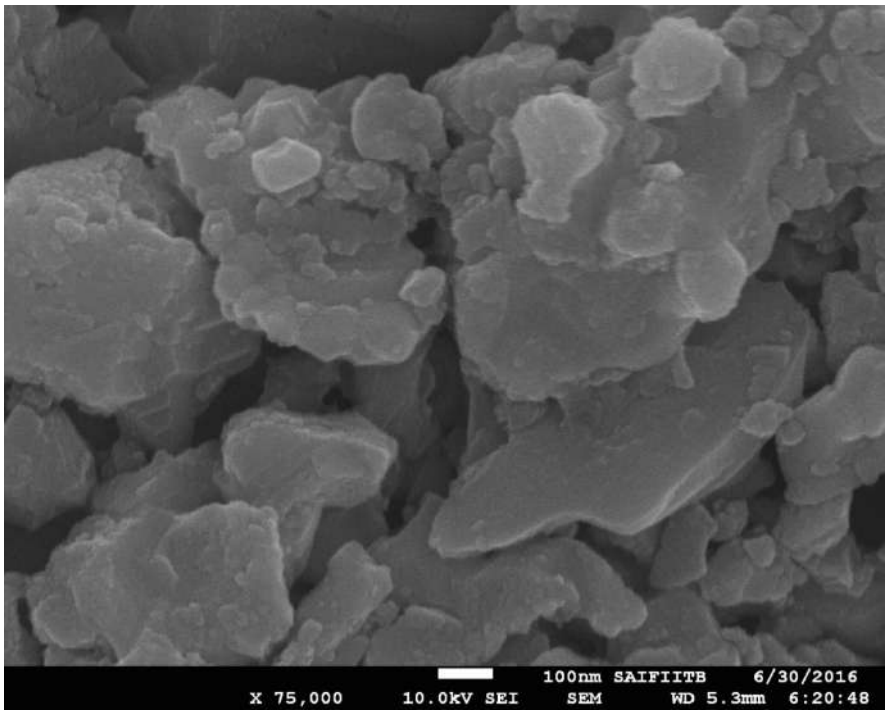


Fig. 4. SEM image of nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$.

3.5 Energy dispersion X-ray analysis

Energy dispersion X-ray analysis (EDX) was investigated the elemental composition of synthesized $Mg_{0.5}Zn_{0.5}Fe_2O_4$ thick film. EDX spectrum of the nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$ is as shown in Fig. 5. The EDX analysis exhibit the presence of Mg, Zn, Fe and O and EDX spectrum reveal almost the same ratio of Mg/Zn/Fe for the nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$ as they were actually added during synthesis process. Hence, confirms the purity of nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$.

ISSN 2454-1974

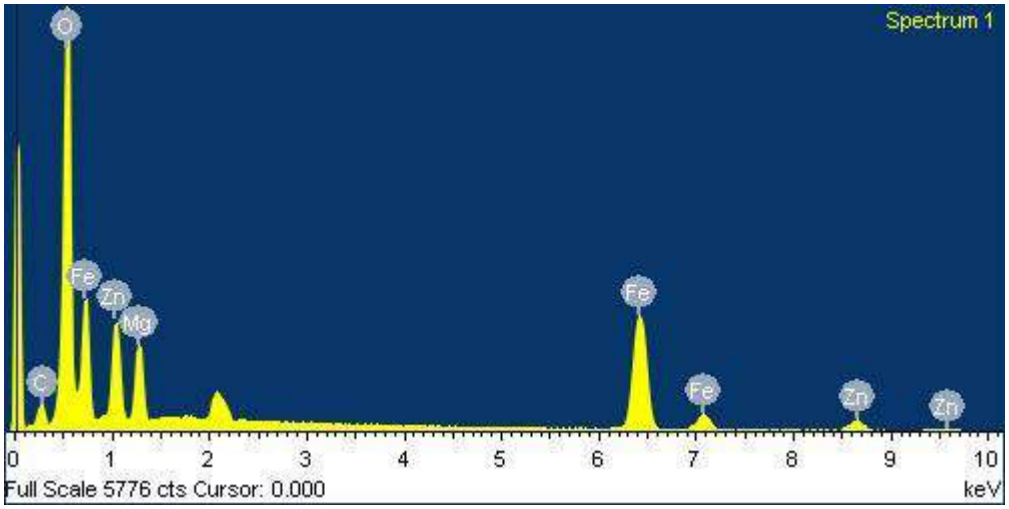


Fig. 5. EDX spectrum for nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$.

4. Conclusions

Zinc doped magnesium ferrite nanoparticles ($Mg_{0.5}Zn_{0.5}Fe_2O_4$) was prepared using less expensive, environment-friendly and low temperature sol-gel method using citric acid as anionic surfactant calcined at 700°C. XRD pattern reveals that the synthesized ferrite consists of nano crystalline particle with average crystallite size 30 nm. The FT-IR spectrum exhibits main absorption bands around 561 cm^{-1} and 437 cm^{-1} corresponding to the vibration modes of the tetrahedral and octahedral sites respectively. The crystallite size from TEM analysis matches well with XRD results confirming the usefulness of sol-gel method for the synthesis of nanocrystalline $Mg_{0.5}Zn_{0.5}Fe_2O_4$. The morphological investigations from SEM showed the sample surface is fully covered by grains with irregular shape. The EDX confirmed the presence of Mg, Zn, Fe and O with values as per the initial precursor concentration.

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Cerium Modified Nanocrystalline $SmFeO_3$ for Ethanol Sensing

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ABSTRACT

Presently, detection of ethanol has become essential in various fields due to its adverse effects on human beings. For selective detection of ethanol, chemiresistive gas sensors are widely investigated. Modified ABO_3 type perovskites have shown their potential in the fabrication of chemiresistive gas sensors. In present work, $SmFeO_3$ perovskite oxide based thick films were fabricated and surface modified with cerium by simple dipping technique. The structural properties of the samples were studied by Field Emission Scanning Electron Microscopy (FE-SEM) and Energy Dispersive X-ray spectrometer (EDS). The results of FE-SEM indicate that average grain size was in nano range and Ce-modified $SmFeO_3$ films were comparatively more porous than pure $SmFeO_3$ film. This porous nature of film favors gas sensing mechanism. The results of EDS suggest that Ce was deposited on the surface of $SmFeO_3$ films. The gas response of pure $SmFeO_3$ film was tested towards LPG, CO_2, NH_3, H_2, C_2H_5OH, Cl_2, and H_2S gases and observed that $SmFeO_3$ film exhibited good response to ethanol (C_2H_5OH). Among modified samples, Ce-modified $SmFeO_3$ film (dipping time 5 min) exhibited excellent ethanol sensing properties such as, maximum response (16.87 at 100^{0}C), response time (24 sec), recovery time (34 sec), excellent stability, and good selectivity towards ethanol. Thus Ce-modified $SmFeO_3$ is a potential material in the fabrication of ethanol sensor. The impacts of Ce modification on the gas sensing performance of the $SmFeO_3$ sensor ware discussed in detail.

Keywords: Gas response, SMO gas sensor, $SmFeO_3$, Surface modification, Sol-gel method.

INTRODUCTION

Development of gas sensors for environmental monitoring has been an active area of research. Among various gas sensors, chemiresistive gas sensors have proved their potential in the detection of hazardous gases. Metal oxide semiconductors have been extensively studied as promising material for selective detection of gases[1-2]. So far, n-type metal oxides semiconductors like ZnO, TiO_2, SnO_2, $LaFeO_3$, and WO_3 were frequently reported for chemiresistive gas sensors[3-7]. They have high sensitivity, low cost and their sensing mechanism is well explained. On the other hand, p-type semiconductors have been relatively less explored for chemiresistive gas sensors. Exploitation of their interactions with target gas may lead to new sensors with enhanced properties.

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$SmFeO_3$ is p-type metal oxide semiconductor usually studied as a chemiresistive gas sensor material for the detection of oxidizing gases[8-11]. It has an orthoferrite phase and ABO_3-type perovskite oxide structure[8]. Its resistance decreases in presence of ozone, oxygen, NO_2, etc. and increases with exposure to reducing gases like ethanol, ammonia, etc. At low temperature, electrical conductivity of $SmFeO_3$ is very small for both oxidizing and reducing gases which results in lack of response. Moreover, $SmFeO_3$ is not stable due to the phase separation of Sm_2O_3 when exposed to reducing gases[12-13]. Due to these two reasons, the applicability of $SmFeO_3$ is limited to detection of oxidizing gases at higher temperature. Now, chemical stability and electric conductivity are related with cations at A and B sites in ABO_3 type perovskite oxide. Therefore doping of $SmFeO_3$ could be an effective approach not only to increase its electrical conductivity but also to use it under reducing conditions. Doping Co, Ni or Mg in $SmFeO_3$ have been attempted to increase electrical conductivity of $SmFeO_3$. But still there is a problem of stability in reduction conduction with these dopants since, Co-O, Ni-O and Mg-O bonds are weaker.

Ethanol is one of the most volatile and flammable gas[14]. It is used in sanitizer, chemical industries and in industrial production. Different organs of the body including the brain can have serious some time permanent damage due to heavy ethanol drinking[15-16]. Therefore, ethanol-monitoring is strongly required. $SmFeO_3$ was reported for ethanol gas detection but optimal operating temperature was very high around 370^{0}C[17-18]. To reduce the optimal operating temperature, Ma Zhao et al. prepared Co-doped $SmFeO_3$ and obtained maximum response to 300 ppm ethanol at lower optimal operating temperature 215^{0}C[19]. Cobalt doping improved electrical conductivity of $SmFeO_3$ but reduced the chemical stability in the reducing environment. S. M. Bukhari *et al.,* investigated that Ce doping in $SmFeO_3$ improved the electrical conductivity and also prevent it from decomposing under a reducing environment[12]. Thus Ce-doped $SmFeO_3$ based gas sensor can be employed for detection of reducing gases like ethanol.

To the best of our knowledge, optimal operating temperature for doped $SmFeO_3$ based ethanol gas sensor was above 200^{0}C and only volume doping was investigated. Therefore in present work, attempt was made to modify $SmFeO_3$ thick films by surface doping with cerium chloride using dipping method. The effect of Ce surface modification on ethanol gas sensing properties of $SmFeO_3$ based gas sensor was investigated. The results depicted that Ce-modified $SmFeO_3$ thick film with dipping time interval 5 min exhibited excellent ethanol response at reduced optimal operating temperature 100^{0}C.

MATERIAL AND METHODS

Fabrication of Thick Films

Pure $SmFeO_3$ powder was prepared by sol-gel method briefly described in our earlier publication[20]. The screen printing method was reported by many authors to fabricate thick films of semiconducting metal oxides[21-23]. Thixotropic paste was prepared from the mixture of the fine powder of $SmFeO_3$ and organic vehicles. This thixotropic paste was then deposited over the glass substrates by using a squeegee. After drying in air, the films were fired at 500^{0}C for half an hour in Muffle Furnace.

Surface Modification of Thick Films

For surface modification, the dipping technique was adopted as reported by some researchers[24]. 0.1 M aqueous solution of cerium chloride was prepared and to this solution $SmFeO_3$ thick films were dipped. The dipping time intervals were 1 min, 3 min, and 5 minute. These films are now identified as “Ce-surface modified $SmFeO_3$ thick films”. They were dried in air for 48 h before their firing in Muffle Furnace at 550^{0}C.

XRD spectrum of $SmFeO_3$ powder was studied to confirm its structure. To observe microstructure and compositions of the films, their FE-SEM with EDS spectra were recorded.

For examining the sensing properties of as prepared thick films, static gas sensing set-up was used which essentially consists of heater mounted on base plate and glass dome. Using silver electrodes, electrical contacts were made with thick film. During the experiment,

the operating temperature was adjusted from room temperature to 400^{0}C. Target gas of fixed concentration (60 ppm) was inserted inside the dome through gas inlet valve using syringe. In the test process, constant voltage was applied to the sensor and the current was measured using digital pico-ammeter in presence of air and the target gases. The gas response is determined from the relation

$$S = \frac{R_g}{R_a} \quad (1)$$

Where, 'R_a' denotes sensor resistance in air and 'R_g' denotes its resistance in target gas at the same temperature[14]. The selectivity of the film is tested against H_2S, LPG, NH_3 CO_2, C_2H_5OH, Cl_2, and H_2.

RESULTS AND DISCUSSION

X-Ray Diffraction Study

XRD spectrum of pure $SmFeO_3$ powder was presented and discussed in detail in our earlier publication[20]. The well defined sharp peaks of high intensity were obtained at 22.94^0, 25.65^0, 31.97^0, 32.71^0, 33.16^0, 46.73^0, 53.26^0, 58.91^0, 68.54^0, and 78.31^0. The corresponding lattice planes were respectively (101), (111), (200), (121), (002), (202), (311), (042), (242), and (421). The results well matches with the standard JCPDS card number 39-1490 and confirmed the perovskite phase with orthorhombic symmetry and Pnma space group. The average crystallite size was calculated using Scherrer's formula

$$d = \frac{0.9\lambda}{\beta\cos\theta}\theta \quad (2)$$

Where 'λ' is wavelength of X-ray, 'θ' is diffraction angle and 'β' is Full Width at Half Maximum (FWHM). The average crystallite size was estimated as d=50.08 nm. The values of lattice parameters 'a', 'b' and 'c' were 5.604 Å, 7.704 Å, and 5.397 Å respectively. The unit cell volume is calculated to be V=233.05 Å^3.

Morphological Analysis

Fig. 1 (A) is the FE-SEM image of pure $SmFeO_3$. Fig. 1 (B-D) are the FE-SEM images of Ce-surface modified $SmFeO_3$ with dipping time intervals 1 min, 3 min and 5 minute.

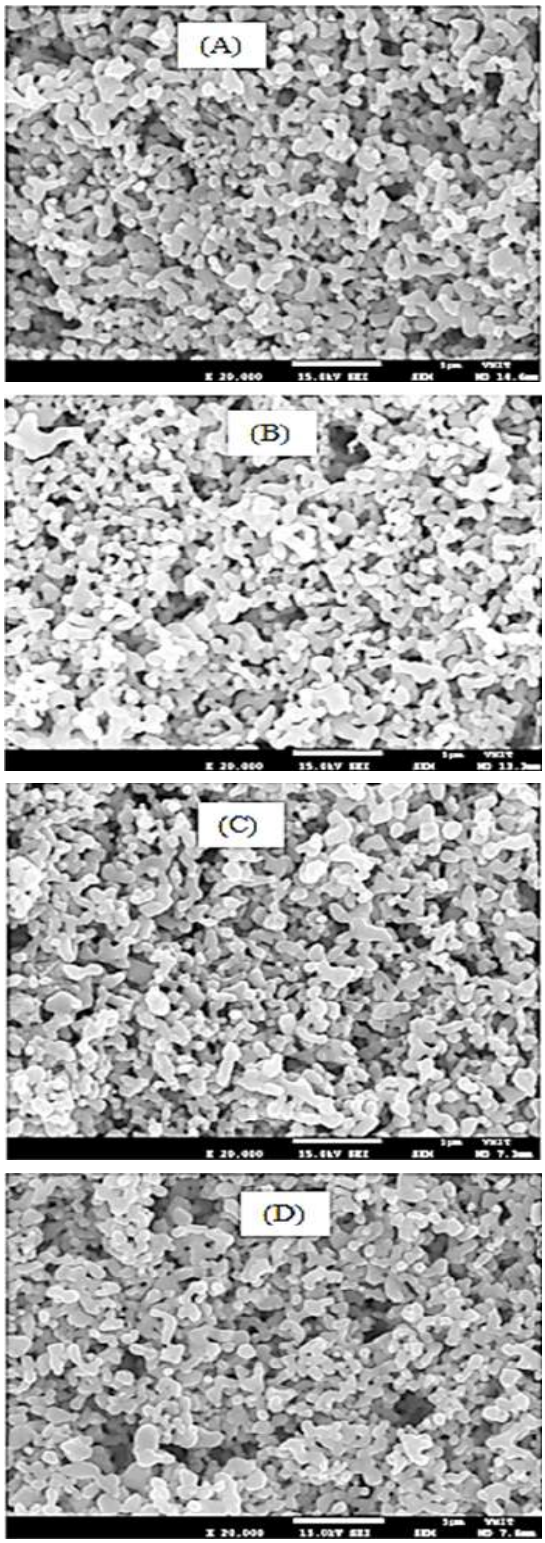


Fig. 1. FE-SEM photographs for (A) $SmFeO_3$ and Ce-modified $SmFeO_3$ with dipping time intervals (B) 1 min, (C) 3 min, & (D) 5 minute

All the images appear to be composed of large numbers of grains concluding the porous nature of the film. The agglomeration of few particles was also observed in Fig. 1(A). The size of $SmFeO_3$ grains ranges from 53 nm to 131 nm. The FE-SEM images for Ce surface modified $SmFeO_3$ thick films seem to be comparatively more porous. Therefore these films favor the adsorption and desorption processes in gas sensing mechanism. Ce particles might be deposited at the inner walls of basic $SmFeO_3$ structure and the formation of Ce particles on the surface of $SmFeO_3$ can be confirmed from the EDS micrographs. Moreover, the number of small Ce particles increases with increasing dipping time. The grain size was observed to be ranges from 55 nm to 69 nm in micrograph depicted in Figure 1(D).

Quantitative Elemental Analysis

Figure 2 presents the EDS spectra of pure and Ce-modified $SmFeO_3$ which shows that Ce was deposited on surface modified $SmFeO_3$ films along with Sm, Fe, and O. Moreover, no other impurities were detected in EDS images of as synthesized thick films thereby indicating purity of samples.

Chemical composition in pure and modified $SmFeO_3$ is displaced in Table 1. It is observed that wt % of Ce increased with dipping time. In Ce modified samples, Ce molecules appear to substitute both Sm and Fe molecules.

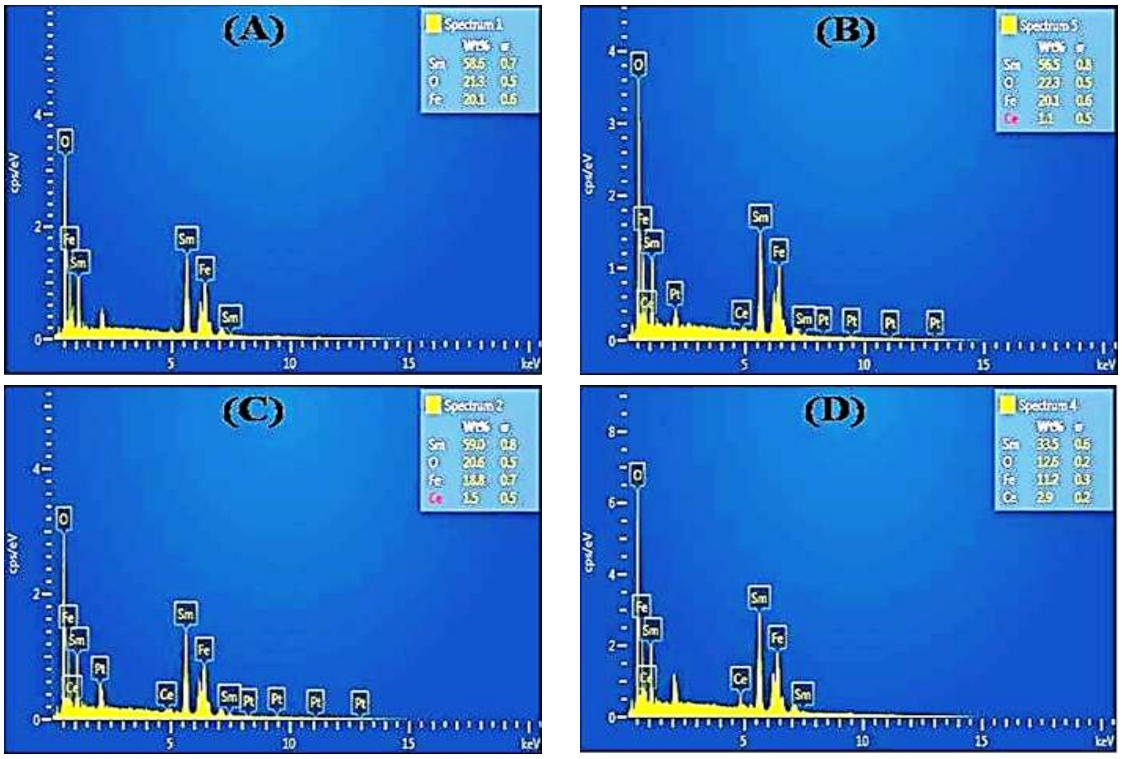


Fig. 2. EDS images for (A) $SmFeO_3$ and Ce-modified $SmFeO_3$ with dipping time intervals (B) 1 min, (C) 3 min, & (D) 5 minute

Table 1: Chemical compositions of pure and Ce-modified $SmFeO_3$ thick films

Samples	Sm (wt%)	O (wt%)	Fe (wt%)	Ce (wt%)
Pure $SmFeO_3$	58.6	21.3	20.1	0
Modified $SmFeO_3$				
Dipping time-1 min	56.5	22.3	20.1	1.1
Dipping time-3 min	59	20.6	18.8	1.5
Dipping time-5 min	53.3	12.6	11.2	2.9

Gas Sensing Performance

Response of pure $SmFeO_3$ film was observed towards different target gases at 100^{0}C and the results indicate that pure $SmFeO_3$ film

was sensitive to ethanol. To investigate the impact of Ce surface modification, gas response of pure and Ce surface modified $SmFeO_3$ films towards 60 ppm ethanol gas was measured by changing the operating temperature from 32^{0}C to 400^{0}C. Pure $SmFeO_3$ thick film showed extremely small response (S=2.07) towards 60 ppm ethanol gas at 300^{0}C. On the other hand, Ce-modified $SmFeO_3$ thick films exhibited improved response and good selectivity for ethanol gas. The change in ethanol gas response according to the operating temperature and gas concentration was investigated for pure and Ce modified $SmFeO_3$ thick films.

Gas Response and Operating Temperature

Figure 3 shows ethanol gas response at different operating temperatures for all the four samples.

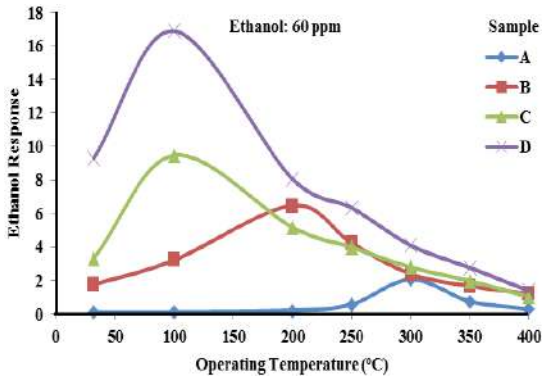


Fig. 3. Gas response for (A) $SmFeO_3$ and Ce-modified $SmFeO_3$ with dipping time intervals (B) 1 min, (C) 3 min, & (D) 5 min towards 60 ppm ethanol

For all the samples, the maximum ethanol gas response was recorded at particular operating temperature below and above which gas response decreased. Maximum response was 6.47 to 60 ppm ethanol for Ce modified $SmFeO_3$ film (dipping time 1 min) and it was observed at 200^{0}C. For Ce modified $SmFeO_3$ films with dipping times 3 min and 5 min, same optimal operating temperature was recorded as 100^{0}C. But, an improved response (S=16.87) was observed when dipping time was 5 minute.

The gas response of $SmFeO_3$ is due to the resistance change that happens in the adsorption and desorption[17-19]. On the oxide surface, adsorption and desorption of ethanol molecules takes place simultaneously. When operating temperature was increase, more and more ethanol molecules were adsorbed and the sensor responses. However, when the temperature exceeds the optimum temperature, adsorption becomes slower than desorption and the redox reaction becomes less intense. Hence decrease in gas response is observed at high temperatures. Generally, resistance of $SmFeO_3$ is affected by doping at Sm or Fe site because of the formation of oxygen vacancies. In Ce-modified $SmFeO_3$ thick film, Ce occupies Sm or Fe or both sites which result in the formation of oxygen vacancies. This promotes oxygen adsorption.

Thus, Ce-modified $SmFeO_3$ film with dipping time interval of 3 min exhibited excellent gas response to 60 ppm ethanol at 100^{0}C.

Gas Response and Gas Concentration

Figure 4 indicates the values of gas response at different ethanol gas concentration for Ce modified $SmFeO_3$ sensor (dipping time 5 min) at 100^{0}C.

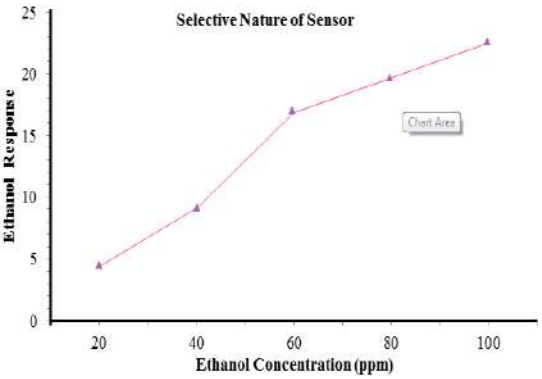


Fig. 4. Gas response for Ce-modified $SmFeO_3$ (dipping time 5 min) for different concentrations of ethanol gas at 100^{0}C

The increase in response, but in a different extent, with increasing ethanol gas concentration was observed. Below 20 ppm, the sensor is almost insensitive to ethanol. This low concentration region known as a cut off region indicates that only few ethanol gas molecules reacts with oxygen species. Hence sensor is almost insensitive to ethanol gas. Good linearity between gas response and ethanol concentration was obtained above 60 ppm because ethanol gas molecules reacting with chemisorbed oxygen species are optimum.

Selectivity of Ce-modified $SmFeO_3$ Thick Film

Figure 5 illustrated the bar diagram indicating responses of Ce-modified $SmFeO_3$ thick film at 100^{0}C towards LPG, NH_3, CO_2, H_2, C_2H_5OH, Cl_2, and H_2S gas. It is clear from the bar diagram that Ce-modified $SmFeO_3$ thick film sensor (dipping time 5 min) was selective to C_2H_5OH gas against

LPG, NH_3, CO_2, H_2, Cl_2, and H_2S gases. This high selectivity to C_2H_5OH gas was attributed to Ce-modification of $SmFeO_3$ thick film. Distribution of Ce particles for 5 min doping favors the adsorption of ethanol molecules as compared to other gases.

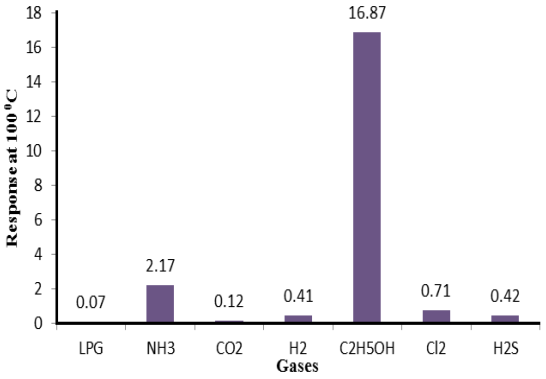


Fig. 5. Selectivity of Ce-modified $SmFeO_3$ thick film (dipping time 5 min) at 100°C

Response-Recovery Profile of the Sensor

Response time is the time taken by sensor to reach 90% of maximum response and recovery time is time taken by sensor to fall to 90% of maximum response. Response-recovery profile for Ce-modified $SmFeO_3$ thick film (dipping time 5 min) to 60 ppm ethanol at 100°C was depicted in Fig. 6. Response and recovery times recorded for as prepared Ce-modified $SmFeO_3$ thick film (dipping time 5 min) sensor were approximately 24 sec and 34 sec respectively.

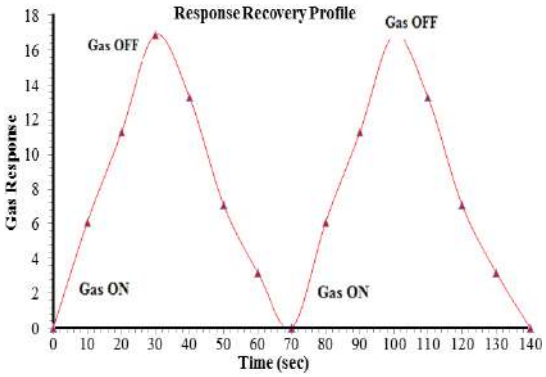


Fig. 6. Response-recovery profiles of Ce-modified $SmFeO_3$ sensor (dipping time 5 min) towards 60 ppm ethanol at 100°C

Stability of Sensor

The gas response of Ce-modified $SmFeO_3$ (dipping time 5 min) sensor to 60 ppm ethanol at 100°C was observed for the period of 90 days. Results depicted in Fig. 7 indicate good stability and durability for Ce-modified $SmFeO_3$ (dipping time 5 min) sensor towards ethanol.

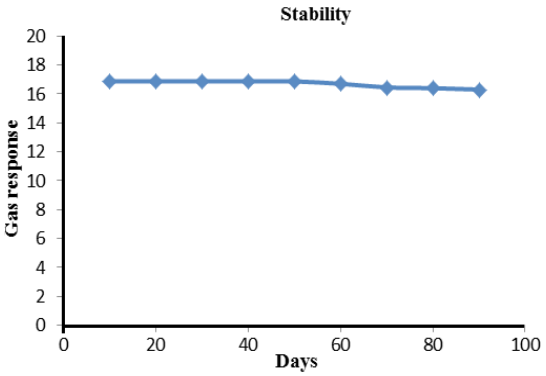


Fig. 7. Stability of Ce-modified $SmFeO_3$ sensor (dipping time 5 min) towards 60 ppm ethanol at 100°C

Ethanol Gas-Sensing Mechanism

Ethanol sensing is based on the resistance change in presence of air and then in presence of ethanol. The change in resistance depends on amount of adsorbed oxygen species on the surface of sensor and the ethanol gas species interacting with chemisorbed oxygen species. Being a p-type semiconductor, holes are the charge carriers in $SmFeO_3$. In presence of air, there is adsorption of oxygen molecules and these adsorbed oxygen trap the electrons from the metal to form highly reactive ionic species like O_2^-, O^- and O^{2-}. The formation of oxygen species depends on temperature and expressed as follows.[25]

$$O_{2(air)} \xrightarrow{upto\ 150^0C} O_2^- \xrightarrow{upto\ 450^0C} 2O^- \xrightarrow{above\ 450^0C} O^{2-}$$

Because of this chemisorption of oxygen molecules, concentration of holes increases. Therefore, hole accumulation layer is formed near the oxide surface and it act as potential barrier between neighboring grains. As a result, sensor has small resistance in presence of air. When such sensor gets contact with ethanol, catalytic oxidation of ethanol takes place producing CO_2 and H_2O. The reaction occurs as follows[26].

$$CH_3\,CH_2\,OH + 6O^- \rightarrow 2CO_2 + 3H_2O + 6e^-$$

During this desorption process, trapped electrons are returned back and the width of accumulation layer decreases. Thus there is increase in sensor resistance in presence of ethanol. The difference between these two resistances produces gas response.

Thus the present work reveals that pure $SmFeO_3$ thick film fabricated by the screen printing

technique, exhibited selective response to ethanol than other tested target gases. All Ce-surface modified $SmFeO_3$ thick films showed improved response to ethanol. Among these Ce-modified $SmFeO_3$ thick films, the sample with dipping time interval of 5 min exhibited excellent ethanol sensing properties such as, maximum response (16.87 at 100^{0}C), response time (24 sec), recovery time (34 sec), excellent stability, and good selectivity towards ethanol. Thus Ce-modified $SmFeO_3$ can be a potential material in the fabrication of ethanol sensor. Dipping technique can be used for the surface modification of $SmFeO_3$ thick film.

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Conflict of Interest

The author(s) declare no conflict of interest.

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CONTENTS

PART A – ENGLISH LANGUAGE PAPERS

Sl.no.	Title and author	Page no.
1	Task-Based Learning in The Indian Classroom: A Comprehensive Exploration | *Dr. Yogesh Pohokar*	1
2	The Importance of Sociology in Higher Education in India: Understanding and Addressing Societal Challenges | *Dr. Devidas Shriram Bhagat*	5
3	A Comprehensive Exploration of Language Teaching Methodologies: From Historical Origins To Modern Applications | *Dr. Ganesh Pundlikrao Khandare*	9
4	Green Chemistry and Sustainable Practices: Reducing Environmental Impact and Resource Consumption | *Dr. Dhanaji Vitthal Jadhav*	14
5	Strategies for Effective Teaching and Learning in Multilingual Classrooms | *Dr. Kishor Jaswantsingh Kshatriya*	18
6	Integrating Mindfulness and Stress Reduction Techniques: A Pathway to Enhancing Students' Mental and Emotional Well-Being | *Dr Chetak Rajendraji Shende*	23
7	Experimental Taxonomic Studies In Genus *Tribulus Terrestris. L* From Marathwada Region Of Maharashtra | *Dr. Kiran Abasaheb More*	30
8	Persian Language Teaching Methodologies | *Dr. Syed Rameez Syed Waseem*	37
9	The Role Of English Language In Promoting Inclusive Education: Strategies, Challenges, And Opportunities | *Prof. Vinod L. Khalatkar*	41
10	Travelogue in English Literature | *Mr. Kashif T. Khan*	44
11	Trend, Issues And Challenges Of Higher Education | *Amit M. Surjushe*	50

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12	The Role of Women in Things Fall Apart: Exploring Agency and Resilience in Igbo Society | *Bhushan Panjabrao Sawale*	58
13	Cross-Cultural Elements in Indian English Prose Writing | *Dr. Gautam Chandrabhan Satdive*	63
14	Challenges & Opportunities in Faculty of Commerce & Managements | *Dr. Santosh B. Gaikwad*	67
15	Concept of Democracy: Democratic Thought, Background and Principles | *Dr. A. D. Jadhao*	70
16	Enterprenurship Capability & Leadership | *Dr.Pankaj Shyamalji Vishwakarma*	76
17	To Study The Status Of Curriculum In Higher Education In Karnataka | *Dr. Shwetha S.P & Prof & Dr: M R Ranganatha*	80
18	Current Trends in Commerce Education | *Dr. Punam Ghisulal Kabra*	89
19	Recent Trends in the faculty of Commerce and Management | *Dr. W. D. Golait*	96
20	Recent Trends and Emerging Technologies in Libraries and Information Science | *Dr Nitesh V Chore*	101
21	"Koha: Open Source Software for Modern ICT Library Management" | *Dr. Rajkumar G. Bonde*	111
22	Globalisation in Higher Education: Challenges and Opportunities | *Lt (Dr.) Devendra Kumar Chauhan*	115
23	New Trends in Commerce Education & Management | *Prof. Dr. Sunil N. Dhere*	120
24	Study on photodegradation of dyes by copper-nickel mixed ferrite - Review | *Santosh M. Arade*	126
25	Subatomic Particle Muon may Change Basic Concepts in Physics | *Swapnil Arsad*	133
26	Ruraland Agriculture Development - A Digital Village | *Dr. Hanumant A Bhosale*	136

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27	Evaluation of a Continuous Assessment and Feedback Concept in Higher Education I *Dr. Elisha Kolluri*	141
28	Synthesis and Characterization of New Chalcones Derivatives with Evaluation of Their Antibacterial Properties I *Mr. Mahendra D. Akkalwar*	148
29	Emotional Intelligence in Higher Education: The Cornerstone for Effective Teaching and Student Success I *Dr. Smita Shingrup, Dr. Mayur Malviya, Dr. Rakhi Malhi*	155
30	Role of Polymer in Pharmacutial Productes I *Mrs. Dipika vikrant Muley, Ms.Shraddha Jaiswal, Mrs.Quddusa Farooqui*	168
31	Advancing Athletic Endeavours: Navigating Challenges & Remedies In Sports And Physical Education Development In Maharashtra I *Dr. Khushal J. Alaspure*	177
32	Psychosocial Factors Influencing Life Satisfaction Among Unemployed Ph.D. Scholars In Maharashtra I *Prashant Sudhakarrao Charjan & Dr. Lumbini Haridas Ganvir*	184
33	A Study of Electronic Commerce in Maharashtra State I *Mr. Sandip D. Bhagat & Prof. Dr. Dilip S. Chavan*	191
34	"Commerce Education" As a Path of Higher Education in India I *Mr. A. R. Pawar*	197
35	Language Teaching Methodologies: An Observation I *Abhiruchi Bhimrao Shejule*	202
36	Laungauge Teaching Methodologies I *Prof Dr. Ajay V.Rele*	205
37	Artificial Intelligence in Higher Education I *Avani Sachin Kulkarni, Anima Dhiraj Sharma, Kesar Shailesh Gagnani*	210
38	Public Library Network System in Maharashtra: Evaluation and Prospects I *Mr. Rajesh O. Gathe & Dr. Rajesh G. Bobade*	218
39	Future of Sports Education in Light of NEP 2020 I *Dr. Umesh Rathi*	223
40	Relationship of Self-Confidence with Aggression and Social Health of Inter University Hand Ball Players I *Dr. Ravijeet O. Gawande*	227

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41	Recent Changes in Legal Framework of India | *Adv. Kavita Aashish Bhattad, Mahima Sanjay Khandekar, Tejal Hemant Gandhi, Vibha Prashant Rathi*	233
42	Recent Developments in Physical Education and Sports : A Brief Outlook | *Dr. Abhay S. Chandekar*	242
43	Recent trend in Behaviour Finance with Reference to factors influencing investment decision in Equity Market | *Saurabh Pandharinath Wagare & Dr Pradeep D. Darvare*	245
44	Study on Recent Trends in Business and Management | *Dr. Gayatri Sureshrao Chawale*	252
45	Recent Trends in English Language Teaching | *Dr. Nilesh P. Sulbhewar*	261
46	Recent Trends in Higher Education in the faculty of Commerce and Management (In the context of Indian Education System) | *Prof. Mahima Sanjay Khandekar, Prof. Tejal Hemant Gandhi, Prof.Vibha Prashant Rathi, Adv. Kavita Ashish Bhattad*	267
47	Recent Trends in Higher Education in the Faculty of Commerce & Management within the Context of India's National Education Policy 2020 | *Prof. Akshay S. Sidam*	274
48	Recent Trends in Higher Education in the Faculty of Humanities | *Dr. Nagorao K. Sore*	280
49	Redefining Movement and Well-being in the Evolving Sports and Physical Education Industry | *Dr. Bhaskar Mahadeorao Sawarkar*	283
50	Study of Clinical & Diagnostic Profile of Patients Suffering from β – Thalassemia in and around Akola Region | *Dr. Tushar G. Deshmukh*	288
51	Improving Higher Education Using the Theory of Relativity | *Mrs Quddusa Kamil Farooqui, Mrs. Dipika Vikrant Muley, Miss. Shraddha D.Jaysval*	301
52	Recent Trends in Higher Education in the Faculty of Commerce & Management | *Dr. Rahul Rajvilas Gadewar*	306
53	Role of Polymers in Cosmetic Products | *Ms. Shraddha Jaiswal, Mrs. Dipika Muley, Mrs. Quddusa Farooqui*	313

Scanned with CamScanner

54	Environmental Effect and Agricultural Application of Zr(IV) and UO_2(VI) Schiff base metal Complexes | *S. R. Kelode*	322
55	Innovative Pedagogy: Online Modules Headmasters Perspective | *Satna Yuwarajsing khojare, Dr. Y. G. Singh*	328
56	Planned to Pollute: The Dark Side of Our Tech Obsession | *Monica Pranav Goud*	333
57	Kamala Das : Confessional Poet of India | *Dr. Anjali P. Pande*	343
58	Artificial Intelligence In Higher Education | *Prof. Tejal H.Gandhi, Prof. Vibha Rathi, Prof. Kavita Bhattad, Prof. Mahima Khandekar*	347
59	English Language Teaching in Indian Rural Areas: Challenges and Opportunities | *Piyush V. Dhale*	354
60	Issues and challenges in higher education: With reference to commerce and management education in India | *Dr. A. M. Dhabalia*	358
61	Effect of Gamma irradiation on pollen viability in *Capsicum annum* L | *Warade C. A*	366
62	Studies of Ground Water Quality of selected area in Umarkhed Taluka Yavatmal District Maharashtra | *Kolapwar Balaji Gangadharrao*	370
63	Emerging Trends And Technologies In Library & Information Services | *Dr. Manoj G. Kadu*	374
64	A Study Of Current Trends In Commerce Education | *Dr. Vikas T. Ninghot*	380
65	Benefits of Clapping Therapy | *Dr. Vikas Tone*	385
66	Anthropogenic Activities Of Different Reservoirs In Washim Region, Maharashtra | *Kshamata Pawar & Dr.P.S.Patil*	389
67	Entrepreneurship skills and leadership skills enhancement with YOGA | *Vibha Prashant Rathi, Adv.Kavita Aashish Bhattad, Mahima Sanjay Khandekar, Tejal Hemant Gandhi*	395
68	Role of Matrices and its Applications in Science and Engineering | *Dr. Mrs. Jayashree S Gawande*	403

Scanned with CamScanner

69	Recent Technological Trends in Higher Education Sector in India | *Dr. Jayaprabha M.Bhagat*	407
70	Resent trends in Higher Education in the Faculty of Life Science and Technology | *Suhas M Pidhekar*	412
71	Diversity of Spiders in Agricultural Fields of Tahsil Patur, District Akola (M. S.) | *Dr. Amit B. Vairale*	419
72	Study Of Sociolinguistic Impact On Aravind Adiga Special Reference To 'The White Tiger' | *Miss Priyanka B. Ruikar*	423
73	Fourier Transforms in view of Trigonometric Inequalities | *Rupesh Rambhau Atram & Dr. Vicky Watkar*	427
74	Preliminary phytochemical screening of stem bark of *Ficus glomerata* Roxb. | *Surve S. V., Wanjare P. D. & Sontakke K.S.*	431
75	Diagnosis of COVID-19 From Chest X-Ray Images Using Deep Learning Approach | *Mr.Siddharth K. Ganvir & Dr.G. K. Reddy*	437
76	Correlation Of Sports Performance With Arm Length, Lower And Upper Arm Circumference Of Ball Badminton Players | *Shri. Sandip Namdeo Kolhe & Dr. Pramod S. Bhalerao*	447
77	A Study of Environment : Issues, Solutions and Its Impact on Human Life | *Sarika Parmeshwar Garole*	452
78	Scope of Online Education in New Education policy 2020 | *Mr.Bhushan Shrirampant Mangate*	457
79	E-Teaching, E-Learning & E-Evaluation in Commerce Education | *Sangita M. Shegokar*	466
80	Enhancing Modern Library Services through the Integration of Artificial Intelligence Tools | *Mr. Shubham Polade & Dr. Vandana Khakre*	470
81	Utopia Within And Without: Dual Facets Of Psychedelic Enlightenment Amidst External Threats In Aldous Huxley's Island | *Smt. Vaishali O. Shelar & Dr. Abhijit R. Aney*	482
82	Status Of English Language In The Scenario Of Globalisation | *Dr. Vijay Baburao Pande*	495

Scanned with CamScanner

83	Recent Trends In Higher Education In The Faculty Of Commerce & Management | *Prof. Sunil Namdeorao Ishwar*	499
84	Introduction To Recent Trends In Physical Education And Sports: Significant Impact On Sports Performance | *Dr. Sushil Battalwar*	506
85	Technology Integration: An Innovative Approach to Enhance English Language Skills | *Dr. Gajanan N. Khamankar*	511
86	A Study On Impact Of E-Commerce On Indian Economy | *Dr. Khushal V. Dhawale*	516
87	The Nature and Acquisition of Language | *Arjun Namdevrao Khobragade*	520
88	The Relationship between Language, Nation and Cultural Identity | *Dr. Savita Yadav*	528
89	The Role of Socioeconomic Factors in Language Acquisition and Development: A Comparative Study | *Mr. Nagesh Wasudeo Ingle*	534
90	Exploring Perspectives of India: A Comparative Analysis between Native and Diasporic Writers | *Dr. Vaibhao B. Pimpale*	540
91	Unlocking Potential: Enhancing Entrepreneurship And Leadership Capabilities | *Bhaskar Sampatrao Ther*	546
92	Artificial Intelligence (AI) Future Propects | *Thakur Suwarnlata Bharat & Dr.Bandini Prem Khdkikar*	551
93	Current Trends In Physical Education | *Dr. Anuragini Rameshrao Bokey*	554
94	Artificial Intelligence and Academic Libraries | *Dr. Nitin S. Satpute*	558
95	From Classroom to Career: The Impact of English Language Proficiency on Employability in India | *Arun B. Chavhan*	566
96	Unveiling the Unseen with Artificial Intelligence | *Dr. P. H. Bhagwat*	570
97	Synthesis of 5-Bromo 2-Hydroxy Chalcones And Their Oxazine and Thizine derivatives | *B.G.Maske, R.R.Wankhade, B.G.Kolapwar, S.M.Khan*	576

Scanned with CamScanner

98	Conflict Between Indian And American Culture With Special Reference To Chitra Banerjee Divakeruni's *Arranged Marriage* | *Prof. Dr. Gajanan P. Hiwase*	581
99	Challenges in Higher Education in India | *Prof.Radheshyam S. Thakare*	587
100	Artificial Intelligence And Higher Education: A Futuristic Approach | *Dr. Anup G. Sharma*	592
101	Contemporary Trends in Higher Education within the Faculty of Humanities | *Jayant Jay & Sonu Meena*	598
102	Nutritional Potentiality and Health Assets of Paddy Straw Mushroom - *Volvariella Volvacea* | *Dilip V. Hande & Anand M. Deshmukh*	604
103	Digital Education Initiatives In India | *Dr. Nilesh V. Gore*	612
104	Knowledge Management in Higher Education |*R. G. Baheti*	619
105	Bridging the Gap: Artificial Intelligence Revolutionizing Commerce Education | *Dr.Tushar Manohar Kotak*	624
106	Consumer Trust in Online Buying Behavior in Yavatmal District | *Dr. Pravin Prakashrao Kulkarni*	632
107	Recent Trends in the Faculty of Commerce & Management | *Ku. Sakshi Pradip Deshpande*	637
108	Recent Trends in Higher Education- A Commerce Education Perspective | *Dr. Dipalee Shah*	641
109	Moisture content and Dielectric Constant of Soil samples from Sinnar Tehsil of Nashik District | *Dr. Dhiware M. D.*	650
110	Recent Trends in Higher Education within the Faculty of Humanities: Navigating the Evolving Landscape | *Dr. Yogesh Dadarao Ugale*	655
111	Changing Nature Of Indian Federal System | *Dr Vijay M. Gawande*	660
112	Remedial Healing Effects Of Nutraceuticals the Golden Spice Turmeric (*Curcuma longa*) - A Gift From Environment | *Dr. Smita Krishnarao Kadwe*	665

Scanned with CamScanner

113	The Role of Women in Indian Sports Culture – A Study | *Dr. Manjusha M. Jagtap*	673
114	Toxicity evaluation of Lead nitrate in the Fresh Water Crab, *Paratelphusa jacquemontii* (Rathbun) | *Nita S. Labhsetwar*	678
115	Butterfly Species Diversity in the Vicinity of Kumbhar kini Dam Darwha, Dist. Yavatmal, (M.S.) | *Dr. Shubhangi V. Gawande*	685
116	AI and Academic Integrity: Ethical Considerations in Research Writing | *Dr. Vivek K. Jagtap*	691
117	Neurosecretory network in central nervous system of *Rhipicephalus annulatus* tick - Histomorphological aspects | *Dr.Pooja S. Thakur*	696
118	A Study of Social Business and Social Enterprising in Maharashtra | *Dr. Suraj K. Rodde*	700
119	The Significance of National Education Policy Frameworks for Higher Education in Sports: Enhancing Sports Performance and Paving the Way Towards Careers | *Dr. Sarojini Umbarkar*	705
120	The Role of Language in Globalization | *Prof. Sangita Virendra Dumore*	714
121	E-Education in Globalization | *Prof. Dr. Nilima D. Ambadkar*	717
122	Emerging Role of AI in Commerce & Management | *Dr. Ambadas B. Pande*	724
123	Environmental Challenges and Sustainable Development | *Farkade A.A. & Sangve K.B.*	733
124	Impact of Healthy Environment on Health: Nourishing The Quality of Life | *Dr. Shyam K. Lande*	740
125	Evaluation of A Continuous Assessment and Feedback Concept in Tertiary Institutions | *ONYEMAH, Lizzy Nkem*	745
126	Evaluation of Continuous Assessment and Feedback in Higher Education: A Comprehensive Analysis | *Jayant Jay & Sonu Meena*	761

Scanned with CamScanner

127	Exploring the Educational Significance: Perspectives of Instructors and Pupils on the Advantages and Functions of Sports in Secondary Education | *Dr. Mahesh V. Rajenimbalkar*	767
128	Exposure to Diverse Linguistic Skills for Students | *Dr. Rakhi J. Malhi*	774
129	Recent Trends in Higher Education in the Faculty of Commerce | *Dr Vinod Ratiram Bansile*	779
130	Bridging Borders, Building Knowledge: Exploring the Landscape of Global Collaboration in Academia | *Dr Narendra Haribhau Shegokar*	786
131	Feminism reflected in Simon de Beauvoir's writings | *Dr. Dipak Uttamrao Ulemale*	793
132	Antimicrobial Activity of Select Aquatic Plants of Painganga River | *Arvind Balasaheb Harkal*	797
133	Changing Role of College Librarian in the *E-Learning* Environment | *Suresh K. Ingle & Dr. Sanjay J. Shenmare*	802
134	Financial Services in Manufacturing Sector in India | *Dr. Praful S.Vairale*	811
135	Intersectionality as a Theoretical Lens to Critical Praxis: Unveiling Dimensions of Identity and Power Dynamics | *Yasmin Chaudhuri*	818
136	Opportunities and Challenges Before the Implementation of New Education Policy (NEP-2020) with Reference to Higher Education | *Ganesh N. Pawar*	830
137	Globalization: It's Advantages and Disadvantages | *Dr. Sandeep B. Agrawal*	837
138	Globalization, Green Economy and Environmental Challenge | *Prof Pradeep Bhalchandra Meshram*	841
139	Green Synthesis and Biomedical Application of Novel Schiff Base Ligand with Transition Metal Complexes | *Gajbhiye R. G.*	851
140	Healthy Body and Peaceful Mind | *Dr. Rakesh A. Badgujar*	860

Scanned with CamScanner

141	Higher Education At Rural Areas: Issues And Challenges | *Dr. Rupesh S. Wankhade*	865
142	Hurdles in Educating English Lingo and Communiqué Proficiency | *Santosh Bhaskarrao Gore*	871
143	Importance of English Language In the Age of Globalization | *Dr. M. V. Ambadkar*	878
144	Utilizing Radiation-Type Boundary Conditions and Gaussian Hypergeometric Differential Equations for Integral Transformation | *Dr. Vicky Watkar & Rupesh Atram*	883
145	Innovative Approaches In Library And Science: A Way Towards Cloud Computing | *Prof. Sidharth A. Patil*	887
146	Innovative Techniques in Teaching Learning and Evaluation: A Pilot Study | *Dr. Sandeep K. Thorat*	892
147	Mind Matters: Understanding multiple intelligences in library and information Science professionals | *Prof. Sushant Khemdasji Maske*	898
148	Recent Trends In Physical Education And Sports: Significant Impact On Sports Performance | *Dr. Sangita N. Lohakpure*	905
149	Diversity Distribution and Density of Araneidae spider around Mahan Dam, District Akola (Maharashtra) | *Sonali. P. Chapke*	910
150	Sustainability of Pisciculture in Digras Taluka of Yavatmal District: Assessment Year 2021-22 | K.A. Tumsare & P.P. Joshi	915
151	Reality in Higher Education In India | *Prof. Dr. Vijay R. Khobragade*	922
152	Language Teaching Methodologies | Ku. Sarika Babarao Zade	927
153	Language Development: An introduction | *Milind Abhimanyu Pathade*	932
154	Language Hegemony and Resistance | *Prof. Borase Jayashri Purushottam*	936
155	Library and information science research trends in Higher Education | *Prof. Dr. Sarla Nimbhoarkar*	946

Scanned with CamScanner

156	Impact of New Education Policy 2020 on Higher Education | *Dr. Madhuri P. Rakhunde*	956
157	Recent Trends In Business And Management | *Prof. Rahul G. Mahure*	962
158	Impact of Management Consultations and Business Solutions on Organizational Performance | *Parikshit S Naik & Dr. Yogesh K. Agrawal*	968
159	Effect of In-doping on structural and optical properties of ZnS thin film | *J.A. Borse*	974
160	NEP-A Vision of a New society | *Dr. Ranjana J. Mahajan*	987
161	Opportunities and Challenges for Social Entrepreneurship in India | *Dr. Pravin B. Jadhav*	992
162	Comparative Study of Aggression and Social Behaviour between Male and Female Boxing Players | *Dr. Pushpalata M. Deshmukh*	999
163	Advancement In Library And Science: A Way Towards Career Growth Of The Students | *Sunil M. Makode*	1006
164	Impact Of Physical Practices In Nourishing Mental And Physical Health: Promoting Fitness And Wellness | *Prof. Gajanan S. Paikat*	1012
165	Testing And Analysis of water sample using physical and biological properties of different area's of Pandharkawada region | *P.B. Rathod, Dr. V. S. Jagtap, C.M. Shahakar*	1017
166	Implications of National Education Policy 2020 and the Role of HEIs | *Dr. K.D. Bompilwar & Dr. S.V. Surve*	1021
167	Synthesis of substituted Quinolines by Friedlander reaction approach under Microwave Irradiation | *Prajakta Mehta, Suchita S. Gadekar, Suryakant B. Sapkal, Jayshree G. Gawai*	1026
168	Relationship Of Kho-Kho Playing Capability With Health Fitness And Motor Fitness Of Boys | *Dr. Kiran G. Pawar & Dr. Jaswant Singh*	1032
169	Pharmaceutical Ethics and Healthcare Justice | *Dr. Vaishali Ravindra Sonawane*	1040

Scanned with CamScanner

170	Policy Framework for Higher Education | *Dr. Sunita Bhoikar*	1050
171	African Silences, an inner voice to save our existence | *Mr. Prakash M. Telgote*	1057
172	To Study the Metal Nanoparticle Synthesis, Characterization, and Optoelectronic Applications |	1061
173	Advanced Microprocessors & Their Applications In Artificial Intelligence | *Kesar S. Gagnani, Avani Kulkarni, Anima Sharma*	1070
174	An Overeview on Nanocrystalline perovskite (ABO_3): A potential material for solid state gas sensor and its applications | *Dr. Manisha S. Pande, Dr. V. D. Kapse, Dr. P. M .Chandak, Dr. T. R. Tatte*	1078
175	Global Perspectives In Competencies To Transform Our Society And Shape Our Future | *Pradeep Gaikwad*	1083
176	Quantitative Assessment of Casein in Various Milk Samples | *S. B. Waghmare[1], T. M. Bhagat, A. P. Mitake, S. P. Rathod*	1085
177	Vermicomposting And Its Importance In Improvement Of Soil Nutrients And Agricultural Crops | *Dr. Ujwala P. Lande*	1091
178	Quality assurance and accreditation in higher education | *Dr. B. S. Kavhar*	1096
179	Smart Supercapacitor: A Conceptual Perspective on Storage Mechanisms, Electrode Materials, Modifications, Types, and Components| *Priyanka S. Dikondwar*	1100
180	Of Prosody a Musical Element: Study of the Pattern of Rhythm and Sound used in Poetry | *Dr. Ganesh Ramdas Khanderao*	1109
181	A Study of the Impact of UPI Transactions on the Growth of the Indian Economy | *Dr. Mayur N. Malviya, Dr. Rakhi Malhi, Dr. Smita Shingrup*	1116
182	Synthetic importance of substituted derivatives of 2-amino-1,3-thiazole based Schiff bases | *P.M. Sonparote and, D. M. Chavhan*	1125
183	Higher Education and Artificial Intelligence: The Present Scenario and Challenges | *Prof. Dr. Ravi Prakash Chapke*	1133
184	Evaluation of Continuous Assessment and Feedback Concept in Higher Education | *Prof. Sarita Uttamrao Chandankar (Chapke)*	1138

Scanned with CamScanner

185	Judicial Activism in India: A Critical Analysis I *Vikram B. Thakre*	1143
186	Dragonfly Diversity around Washim region of Maharastra, India I *Shubhangi Gautam Gudade & P.S.Patil*	1145
187	Review on: Recent Advances in Synthesis of Selenium Nanoparticles and its Therapeutic Applications I *Jedhe V. S., Adole S.D. Patil S. M. and Mehere B. A.*	1150
188	Multi-scale Morphological Edge Extraction by Thersholding I *Dr. Manish L Jivtode*	1171
189	Formulation and Evaluation of Ophthalmic In Situ Gel I *Saloni Sanjaykumar Redasani, Dr.A.M.Mahale*	1176
190	Emerging Trends in English Literature Teaching I *Asst.Prof. Pravin Kanake*	1185
191	Embracing Global Perspectives in Higher Education: A Comprehensive I *Dr. A. D. Jadhao & Prof. Vijay B. Rathod*	1188
192	Addressing Issues, Challenges and Remedies in Higher Education within the Faculty of Science I *S. V. Jadhav, P. R. Jagnit & Y. I. Biradar*	1191
193	Artificial Intelligence in Libraries I *Anima D. Sharma, Kesar S. Gagnani & Avani S. Kulkarni*	1199
194	Teaching, Research and an Overview upon Contemporary Higher Education in India and Across the World I *Dr Savita Digambar Jogdande*	1207
195	Use of Information Communication Technology (ICT) and Library I *Dr. Shyam Ramrao Dutonde*	1211
196	Exploring Recent Trends in Social Sciences I *Prof. Dhairyshil Prushottam Taksande*	1214
197	Current Trends of "Nanotechnology" in Pharmaceutical I *Mr.S. M. Ikade*	1221
198	Development of Lung diseases monitoring system in soft computation by using IOT I *Rashmi A.Charjan, Dr.Ajit kumar, Dr.G.K.Reddy*	1229
199	Artificial intelligence and its scope in different areas with special reference to the field of education I *Prof. Dr. Dipali T. Deshmukh*	1234

Scanned with CamScanner

200	Crisis Management In Higher Education | *Dr.P.N. Ladhe*	1243
201	The Evolution and Impact of E-commerce in India | *Aditya Chandrakant Nawgrahe*	1247
202	Challenges And Opportunities In Implementing Digital Transformation In Commerce | *Prof. Dr. Haridas Manikrao Dhurve*	1251
203	Biodiversity Aquatic Weeds In Washim Region Of Maharashtra, India | *Achal Gautam Gudade and P.S.Patil*	1259
204	Teaching English Pronunciation through Task Based Language Learning | *Dr. G.B. Mane*	1264
205	Discoloration Of Head In Sorghum Due To Curvularia Lunata | *Dnyaneshwar K. Sherkar, Sonali A. Tayde, Madhuri S. Hingankar and Megha R. Solanke*	1267
206	Formulation and Evaluation of Liqui-Pellet: The Emerging Next-Generation Oral Dosage Form | *Vaishnavi V Tawde , Dr. A. M. Mahale*	1272
207	Artificial Intelligence in Indigenous Knowledge and Practices: A comparative Analysis | *Oluwatoyin Mary Yerokun*	1282
208	Diversity of Arbuscular Mycorrhizal Fungi and their Symbiotic Association with *Salvia splendens* | *Pooja K. Dhawale & Rekha C. Maggirwar*	1291
209	Formulation And Evaluation Of Diclofenac Sodium Microspheres : An Multiparticulate Drug Delivery System | *Manisha Maroti Thakare*	1295
210	Technology Integration in Higher Education: Life Science and Technology | *Narendra Manwar & Suhas M Pidhekar*	1304
211	Ichthyofaunal diversity of freshwater fishes from the Washim District, Maharashtra, India | *Aarti D. Gore, H. V. Wanjari, S.D. Rathod, P.S Patil and Sawaikar, K.S*	1310
212	The Global Perspectives In Jhumpa Lahiri's Works | *Dr. Priyamvada Dinesh Bhat*	1316
213	Globalization of English Language and Its Impact on Indian Regional Language and Culture | *Dr. Meenakshi V. Wasnik*	1320

Scanned with CamScanner

214	The Study Of New Education Pollicy [NEP] 2020 On Impact Of Higher Education I *Pooja Purushottam Ghulaxe*	1326
215	Detrimental Impacts Of Globalization On The Environment I *Ms. Apeksha Ghanshyamji Dubey*	1332
216	Nanoformulated Tamarindus indica Extract: A Novel Approach for Anthelmintic Therapy I *Apeksha G. Toshniwal*	1335
217	Study of Diversity of Reptiles in Ralegaon region District Yavatmal, Maharashtra, India I *Dr.S.D.Dawada, Bhagyashree Lohakar & Narendra Manwar*	1342
218	Land use & Land Cover Study by Using RS & GIS: Study Area Aurangabad (MS) I *Dr Jayendra C. Wasnik*	1349
219	Impact of New Education Policy 2020 on Higher Education I *Dr. Jayashri P. Kale & Asst. Prof. D.S.Kavar*	1354
220	Importance Of Nanotechnology In Pharmaceutical Formulations I *Venkatesh Nandkumar Nalabale*	1362
221	Higher Education in India: A Study of Paradigm Shift I *Dr Durgesh Vitthal Borse*	1372
222	A Study On Online Shopping In India – An Overview I *Dr. Vrishali Kakasaheb Madne*	1377
223	Formulation And Evaluation Of Fast Dissolving Oral Films I *Shubhangi Vilas Jadhao*	1383
224	Recent advances of nanotechnology in pharmaceutical field I *Shalini Ulhas Rathod & Narendrakumar D. Phupate*	1395
225	Advanced Approaches In Physical Education And Sports: Trend In Modern Era I *P. B. Gaikwad*	1406
226	Global Issues Of Existentialism And Existential Crisis In The Plays Of Vijay Tendulkar I *Ms. Swati Ramesh Raut & Dr. Pritee D. Thakare*	1412
227	Contradiction in NEP 2020 Policy and Credit Framework of Higher Education in Relation to Status English Language I *Dr. Syed Imtiaz Jukkalkar*	1415
228	The Impact of Globalization on the Environment: Challenges and Solutions I *Mr.Abhyuday Anant Somwanshi*	1420

Scanned with CamScanner

229	Technological Integration In Higher Education I *Dr. A. Y. Ali*	1425
230	Studies And Assessment Of Water Quality Parameters Of Akola District Region (Maharashtra) I *S.J.Patil*	1430

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An Overeview on Nanocrystalline perovskite (ABO_3): A potential material for solid state gas sensor and its applications

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FULL PAPER

1. Introduction

In day today modern life detection of different gases play a vital role. The significant area of research towards gas sensing that leads to the fabrication of gas sensing devices which detect various harmful gases. Human body suffers from different diseases due to the emission of various toxic and hazardous gases. Solid-state sensors are among the most versatile of all sensors, as they detect a wide variety of gases, and can be used in many different applications. Among the unique attributes of the solid-state sensor are the abilities of the sensor to detect both low ppm levels of gases, as well as high combustible levels. Solid state gas sensors, are the excellent candidates to the fabrication of commercial gas sensors for a wide range of applications [1-5]. The development of high precision gas sensors is crucial for the monitoring of harmful (exhaust) gases in the environment. A variety of dangerous gases, such as CH_4, NO_2, LPG, NH_3, SO_2, CO, H_2S, NO_2, Acetone, H_2, ethanol, and methanol, are constantly released by industry, transportation, and agricultural activities. Many of these gases are hazardous to human health as well as the environment, even at levels measured in parts per million, or ppm. Some of these gases, like H_2, are naturally explosive when exposed to air.

In recent years, nanomaterials based on perovskite have been used in a variety of sustainable applications. Their structural properties enable researchers to investigate functionalities in a variety of directions, including solar cells, LEM devices, transistors and sensors, etc. Perovskite nano-materials have been shown to have

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remarkable sensing performance to a wide range of chemical and biological species, both in solids and solutions. In particular, they are able to detect small molecules (e.g., oxygen, nitrogen dioxide, carbon dioxide, etc.). In addition, Solid-state gas sensors are emerging as a viable substitute for the intended real-time functions in light of recent developments in the material sciences and advancements in processing and downsizing techniques. The greatest options for the development of commercial gas sensors for a broad range of such applications are solid state gas sensors, which are based on a variety of concepts and materials. [6-10].

2. Structure, Stability and Properties of Perovskites

Perovskite is the name given to the compounds that have the formula type ABX_3 with different sized 'A' and 'B' cations bonded to anion X [11]. ABO_3 Perovskites exhibit good thermal stability with an eV band gap of 3–4, which is why they were used in a lot of gas sensing studies [12]. Perovskite materials can be employed as sensors for gaseous species because their stability was significantly disrupted when exposed to gaseous environments, such as NO_2, CH_4, NH_3, C_2H_5OH, acetone, etc. [13]. The chemiresistive I–V, phosphorescence, and fluorescence responses of these perovskite materials can be used to record the sudden changes in them. However, in these sensing investigations, the opto-electronic characteristics of perovskites are crucial. Renowned contenders with remarkable attributes including electrical conductivity, ferroelectricity, superconductivity, catalytic activity, etc. are perovskite oxides. There are several ways to synthesis the naocrystalline perovskite material, including the hydrothermal, sol-gel, and chemical co-precipitation processes, etc. Because of the remarkable stability of the perovskite structure, structural flaws can be created when one or both of the cations in the A and B sites are partially substituted with other metals that have a different oxidation state.

3. Applications of Perovskite materials

The desirable characteristics of perovskites contributed to a significant development in research in recent years, indicating a genuine interest in the possible uses of these materials. They consist of, but are not confined to:

- Superconductivity
- Characteristics of catalysis
- The unique characteristics of optoelectronics.

Numerous companies are interested in using perovskites and are working to further the technology through research. Photovoltaics and optoelectronics are two companies that are particularly interested in perovskites:

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Solar energy

Since they are cheaper for production as well as greater flexible qualities than conventional silicon solar cells, perovskite materials present a possible substitute. Perovskite-based solar cells have demonstrated significant commercial promise in recent years, with their efficiency rising to above 25% in lab settings. The resilience and lifetime of these solar cells are presently being researched.

LED

LEDs have been around for many years, but the next generation of this technology will be offered by perovskite-based LEDs. Perovskite materials' optoelectronic qualities, which include their high photoluminescence quantum yield, tunability, and less expensive manufacture, have attracted the attention of numerous scientists and technological businesses.

4. Review of solid state gas sensor

Soil, water, and air pollution are the three categories into which environmental contamination falls. Of these three categories, air and water pollution are the main contributors to disasters since they spread quickly over a wide area in a short amount of time. Since industrial progress has dramatically expanded environmental pollution to such a level that public concern is now so great that it cannot be ignored any longer, environmental monitoring and management are absolutely necessary. Therefore, in order to address these environmental issues, thorough study has been done to quickly identify these contaminants and lower their levels to within the regulatory allowed concentrations. These factors have contributed to the advancement of solid-state gas sensor research and development in recent years. Gas sensors with metal oxides as the sensing medium have been widely used in gas detection applications. In fact, there is growing interest in gas sensing for nanocrystalline semiconducting metal oxides with regulated compositions, which also represent an intriguing new area of fundamental research [14]. Because of its oxide stability, high response, low production cost, and ability to respond to a wide spectrum of chemicals, semiconductor metal oxide nanostructures are the most preferred of all the solid state gas sensing materials. They respond quickly, are robust, dependable, and reasonably priced. Different types of solid state gas sensors are semiconductor gas sensor, optical gas sensor, electrochemical gas sensor, etc. Semiconductor gas sensors (SGS), known sometimes as chemoresistive gas sensors, are typically based on metal oxides (e.g. SnO_2, TiO_2, In_2O_3, WO_3, NiO, etc.). Recent applied research and product releases in this sector of gas sensors have revealed some noteworthy developments regarding the use of nanotechnologies and gas-sensing layers. In the sensing industry, optical gas sensors are crucial for measuring chemical and biological quantities. Changes in the absorption spectrum were used to measure the first optical chemical sensors. Chemical sensors and biosensors currently employ a wide range of optical techniques, such as

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ellipsometry, surface plasmon resonance (SPR), spectroscopy (luminescence, phosphorescence, fluorescence, Raman), interferometry (white light, modal, and optical waveguide structures), spectroscopy of guided modes in optical waveguide structures (grating coupler, resonant mirror), and interferometry (white light, phosphorescence, and fluorescence). Electrochemical gas sensors use an electrochemical cell, which is made up of two terminals (an anode and a cathode) of the same composition and a casing that holds a collection of chemical reactants (electrolytes or gels) in contact with the environment. A membrane on the top of the gas sensor enclosure allows the gas sample to pass through it. At the anode, oxidation happens, and at the cathode, reduction happens.

5. Conclusion

In this review study, the materials chosen for the construction of such gas sensors, and the sources of emission and regulatory standards of air pollutants are briefly reviewed. It has been addressed how advances in material science have led to the development of potential solid-state gas sensors, with the aim of comprehending the underlying technology and offering targeted functionality for a particular application. Perovskites are an extremely interesting and diverse class of materials which exhibit many useful characteristics that are determined by their composition. In the current research, we examine recent advancements in perovskite-based materials with excellent characteristics for application in optoelectronics and photovoltaics.

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18. **A Study of New Education Policy-2020 Challenges of Teachers and Students** 86-88
Dr. Saddam R. Sayyad

19. **Impact Of National Education Policy 2020** 89-92
Dr.P.N.Ladhe

20. **NEP 2020: A Tool To Make India Superpower** 93-97
Dr.Gayatri Sanjay Tiwari

21. **A Review of Principles and Issues of NEP 2020** 98-102
Dr. Anand P. Wadwale

22. **Value Education and Teacher** 103-10
Dr. Bapurao Dinaji Watode

23. **National Education Policy 2020: A Concern for Higher Education and Management Education** 108-11
Dr. Gayatri S. Chawale

24. **NEP 2020 and Higher Learning Institutions: A Comprehensive Analysis of College Involvement** 113-11
Dr. Lalchand Damodar Bodile

25. **Skill Enhancement and Teachers in Education** 118-122
Dr. Pravin P. Kulkarni

26. **A Critical Study Of NEP 2020: Issues, Approaches, Challenges, Oppertunities And Criticism** 123-128
Dr. Subhash P. Jadhao

27. **New Educaton Policy 2020 and Its Challenges** 129-132
Ms. Komal Ashok Gupta

28. **A Comparative Study of Old Education Policy and New Education Policy 2020** 133-137
Mr. Bhushan Shrirampant Mangate

29. **National Education Policy 2020: A Concern for Management Education** 138-142
Prof. Dr. Rupesh M. Kurhekar

30. **Indian Higher Education and its Challenges** 143-147
Prof. Rahul Gayakwad

31. **Environmental Attunement In Yoga, Physical Education And Sport** 148-151
Dr. Sandeep Gadadane

32. **Exploring All the Features And User Concerns Of Home Away Your Ultimate Housing Solution** 152-161
Anupam Pandey, Yash Bambal, Sakshi Bhor, Karn Datta Godse

33. **New Education Policy 2020, A Journey Toward A More Holistic and Multidisciplinary Education** 162-165
Dr. B. N. Mahajan

34. **National Education Policy 2020: A Catalyst for Skill Based Education** 166-170
Dr. Shivcharan. L. Kottewar

35. **Upcoming Challenges of New Education Policy 2020** 171-174
Dr. Vivek H. Meshram

Upcoming Challenges of New Education Policy 2020

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Abstract:

A new education policy was implemented with comprehensive provisions for the holistic development of the student. Indian education has completely changed since the education policy of 1968 till now and it will be a challenge to make the new education policy-2020 successful by accepting the change. India's basic problems of unemployment, illiteracy, poverty, improvement of standard of living can be reduced to some extent by accepting the challenges that come after the implementation of the new education policy. There is no doubt that the new education policy is more comprehensive than the old education policy, but only if it is effectively implemented, Indian education will change for the better and the nation will progress and India will become a super power in terms of knowledge globally.

Keywords: Holistic development, basic problems, comprehensive, super power

Introduction :

The NEP 2020 is the first education policy of the 21st century and replaces the thirty-four year old National Policy on Education (NPE), 1986. Built on the foundational pillars of Access, Equity, Quality, Affordability and Accountability, this policy is aligned to the 2030 Agenda for Sustainable Development and aims to transform India into a vibrant knowledge society and global knowledge superpower by making both school and college education more holistic, flexible, multidisciplinary, suited to 21st century needs and aimed at bringing out the unique capabilities of each student. The national education policy 2020 aims at making our home country a global choice for education by providing high quality, different variety and dynamic education hub to all the people in abroad.

India's incredible diversity as well as a blunt and outdated education system make implementing a new policy a daunting task. India has the second largest education system in the world. According to the AISHE 2019 report, India's higher education sector has 3.74 crore students in nearly 1,000 universities, 39,931 colleges and 10,725 independent institutions. Thus, nationwide implementation of this mega education policy at the state, district, upazila and taluka levels is going to be a big challenge.

Major challenges of NEP 2020

1) **To set up world class universities is a difficult task:** India today has about 1,000 universities across the country. Achieving this goal of doubling the gross enrolment ratio in higher education by 2035 will require the establishment of universities in the next 13 years with a reach from big cities to villages. Opening a university that provides good infrastructure and imparts quality education is undoubtedly a big challenge in the coming times.

2) **Low performance of Indian universities in research area:** As per the new policy, reputed

foreign universities will come to India but the question is whether our traditional university can achieve or maintain the same high performance level as the foreign university.

3) **Changing the mindset:** The current education system is a hangover of the British and Industrial age. The change in mindset will involve two or more generation of parents, teachers, grandparents and educators. A STEM education focused generation has to give way to the NEP. The corporate world also will need to align this and change its recruitment and grooming policies. There will be several challenges in changing this mindset. However, it can be done with lot of soft power play by the government.

4) **Problems in reforms to our school system:** The National Education Policy 2020 aims to re-introduce 2 crore non-current students into the school system. To accomplish this in the next 13 years, investment will be required in increasing the number of schools along with infrastructure and recruiting qualified teachers in appropriate numbers.

5) **Funding is a big challenge:** The Kothari Commission had recommended spending 6 percent of GDP on education. But till today we could not reach that height. The National Education Policy envisages an increase in education expenditure from 4.6% of GDP to 6% in 2020, which is about INR 2.5 lakh crore per year. Balancing spending on education with other essential expenditures like health, planning, national security is certainly challenging.

6) **Bottom-up approach:** As Indians, we are socially programmed to accept top-down approach in all areas of life. This social and educational transformation is only possible with a bottom-up grass-root level intervention. In the grand scheme of things, an important action would be to repair and revamp the system through a bottom-up approach and bring a definitive change in the mindset of the stakeholders, including the office staff and parents, right at the outset. A transformation is needed from 'what to think' to 'how to think'.

7) **Need to create a large pool of trained teachers:** In school education, a comprehensive restructuring of the curriculum in policy is a very welcome step. But to deliver this curriculum effectively, we need teachers who are trained and understand the educational needs. A new change in the curriculum requires a change in the mindset of teachers as well as parents.

8) **Language barrier:** Education in mother tongue till class V is also a point of contention. It is true that good comprehension is in language and is important for future progress. If the foundation is not strong, even good teaching and infrastructure are of no use. But it is also true that the main goal of education is social and economic mobility and the language of mobility in India is English. Further distancing from English as a global language can have serious consequences.

9) **Multilingualism debate:** Home language succeeds in places where the ecosystem extends all the way through higher education and into employment. Without such an ecosystem in place, this may not be good enough. The NEP speaks of multilingualism and that must be emphasised. Most classes in India are de facto bilingual. Some states are blissfully considering this policy as a futile attempt to impose Hindi.

10) **Pedagogical limitations:** The document talks about flexibility, choice, experimentation. In higher education, the document recognizes that there is a diversity of pedagogical needs. If it is a mandated option within single institutions, this will be a disaster, since structuring a curriculum for a classroom that has both one-year diploma students and four-year degree students' takes away from the identity of the institution.

Initiatives by government to promote Online education

The government of India is imagining and shaping E-learning with digital pedagogy as a long

erm strategy in the Education sector. Government has proposed several channels for extensive sources of digital education through its different initiatives. Every State/UT has taken various inclusive steps to bridge the digital divide and bring out digital literacy among the students. Some State governments have initiated providing smartphones and tablets to promote Digital Education.

1) **PM E-Vidhya:** It is a comprehensive program announced on 17 May 2020, with the objective to unify digital and online education with the education programs for better reach and access to E-learning. It targeted almost 25 crore school students across the country.

2) **DIKSHA (Digital Infrastructure for Knowledge Sharing):** Digital Infrastructure for Knowledge Sharing was initiated in 2017 with the dream of 'One Nation, One Digital Platform.' The goal of this platform is for providing quality e-content in the form of e-textbooks and audiobooks for free to all teachers and learners across the country.

3) **SWAYAM Prabha TV channel: This initiative include 34 channels that focus on educational programs for classes 1 to 12 with objectives of "One class, One channel".** The quality educational programmes with class-wise content are delivered on a 24x7 basis using GSAT-15 satellites. It has a tie-up with Tata sky and Airtel to air and telecast the educational programs.

4) **VidyaDaan:** With the objective to seek donations and contributions for the digital education resources for the school from educational institutions, private players, and individuals, VidyaDaan was launched in April 2020. Assam, Goa, Kerala, Odisha, UP, Punjab, Maharashtra, Gujrat, Telangana, and Chandigarh along with the CBSE and NCERT are working efficiently on VidyaDaan to source content on DIKSHA.

5) **Digitally Accessible Information System (DAISY):** Special e-content for visually and hearing impaired developed on Digitally Accessible Information System (**DAISY**) and in sign language on NIOS website/ YouTube

6) **SWAYAM (Study Webs of Active Learning for Young Aspiring Minds):** Under the 'Digital India' Initiative of Government of India, one of the thrust area is 'Massive Online Open Courses (MOOCs)'.MHRD, Government of India has embarked on a major initiative called 'Study Webs of Active Learning for Young Aspiring Minds' (SWAYAM), to provide an integrated platform and portal for online.

7) **National Academic Depository (NAD):** The vision of National Academic Depository (NAD) is born out of an initiative to provide an online store house of all academic awards. National Academic Depository (NAD) is a 24X7 online store house of all academic awards viz. certificates, diplomas, degrees, mark-sheets etc. duly digitised and lodged by academic institutions / boards / eligibility assessment bodies. NAD not only ensures easy access to and retrieval of an academic award but also validates and guarantees its authenticity and safe storage. National Academic Depository comprises of two interoperable digital depositories viz. CDSL Ventures Limited (CVL) and NSDL Database Management Limited (NDML). These digital depositories have ensured hardware, network facilities and software of prescribed quality for smooth and secured operationalisation of NAD.

8) **National Digital Library of India (NDL India):** National Digital Library of India (NDL India) is an all-digital library that stores information (metadata) about different types of digital contents including books, articles, videos, audios, thesis and other educational materials relevant for users from varying educational levels and capabilities. It provides a single-window search facility to access digital contents currently existing in India as well as other digital sources under a single umbrella.

) Academic Bank of Credit (ABC): Academic Bank of Credits(ABC) is an educational digital platform which would facilitate seamless mobility between or within degree-granting Higher Education Institutions (HEIs) through a formal system of credit recognition, credit accumulation, credit transfers, and credit redemption to promote distributed and flexible teaching and learning.

0) DigiLocker : DigiLocker is a platform for issuance and verification of documents & certificates in a digital way, thus eliminating the use of physical documents. Indian citizens who sign up for a DigiLocker account get a dedicated cloud storage space that is linked to their Aadhaar (UIDAI) number. Organizations that are registered with Digital Locker can push electronic copies of documents and certificates (e.g. driving license, Voter ID, School certificates) directly into citizens lockers. Citizens can also upload scanned copies of their legacy documents in their accounts. These legacy documents can be electronically signed using the eSign facility.

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117	Women Empowerment Through Higher Education In India *Miss Priyanka Mahendrasing Pardeshi & Dr. Avinash Nile*	703
118	Dynamics of English Language Diversity: Exploring Variations, Influences, and Evolution I *Dr. Vivek Harichandra Meshram*	707
119	Travel from Textbook to AI: Role of Social Media and AI in English Language Teaching and Learning I *Ms Vinothini M & Dr Benzigar M*	713
120	To Study the Role of Chemistry in Environmental Protection: Review I *Mr.Khatke Tukaram E.*	719
121	The Changing Role Of The English Language In The Era Of Globalization I *Dr. D. B. Wankhade*	730
122	Beneath the Surface: A Comprehensive Analysis of Mycorrhizal Root Colonization In *Andrographis paniculata* I *Dongare S.B.*	734
123	Social Business & Social Entrepreneurship *Dr. Rahul Kacharu Binniwale*	743
124	"Nanoformulated Tamarindus indica Extract: A Novel Approach for Anthelmintic Therapy" I *Apeksha G. Toshniwal*	745
125	Comparative Study Of Benincasa Hispida Extract And Its Silver Nanoparticles As The Anti-Obesity Effect. I *Likha Dyli*	752
126	Synthesis Of Some Novel *S*-Arylisothiocarbamides *Dr. Reena J. Deshmukh*	764
127	Understanding Global Perspectives in Higher Education: Addressing Issues, Challenges, and Solutions" I *Shameena Bano*	768
128	Vocational Education: Scope and Challenges in National Education Policy-2020 I *V.D.Jadhao*	777
129	Need Of Library Automation Incurrent Era: A Study I *Prof. Swapnil Haribhau Dandade*	783
130	Formulation And Evaluation Of Aceclofenac Bionanocomposite By Using Mind Method I *Pankaj Vaijanath Maske & Dr. P. S. Kawtikawar.*	787
131	Formulation And Evaluation Of Lansoprazole Gastroretentive Floating Films I *Prajwal Sanjay Milkhe & Dr. A.A.Harsulkar*	798

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Dynamics of English Language Diversity: Exploring Variations, Influences, and Evolution

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Introduction:-

The global prevalence of English as a lingua franca has led to a rich tapestry of linguistic diversity. This paper delves into the intricate dynamics of English language variations, influences, and its evolutionary trajectory. Against the backdrop of a rapidly changing world, understanding the nuances of English language diversity becomes imperative for effective communication, cultural appreciation, and educational strategies. English, as a global language, manifests in diverse forms influenced by regional dialects, socio-cultural contexts, and historical developments. The increasing interconnectedness of societies through globalization and technological advancements further amplifies these variations. Exploring the intricate layers of English language diversity is not merely an academic pursuit but holds practical implications for cross-cultural communication, language education, and social integration.By unraveling the complexities of English language diversity, this research aims to contribute valuable insights to linguistic studies, cultural anthropology, and educational practices. The findings hold relevance for educators, policy-makers, and individuals seeking a nuanced understanding of language in a globalized context.

Literature Review:-

The literature review section of "Dynamics of English Language Diversity: Exploring Variations, Influences, and Evolution" provides a comprehensive examination of existing scholarly works, theories, and research findings related to English language variations, influences, and evolution.

English Language Variations:

Numerous studies have explored regional and socio-cultural variations within the English language. Smith (2018) delved into the diverse dialects across the United Kingdom, highlighting the nuanced linguistic landscapes. Additionally, Schneider's (2015) work on World Englishes offered insights into variations emerging from global contexts.

Influences on English Language Diversity:

Understanding external influences on English language diversity is crucial. Crystal (2019) outlined the impact of globalization on language, emphasizing how

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increased interconnectedness shapes linguistic evolution. Furthermore, Coupland's (2020) research delved into the role of migration in influencing linguistic diversity.

Evolution of English Language:

The historical evolution of English has been a subject of extensive research. Baugh and Cable's (2018) seminal work, "A History of the English Language," provides a comprehensive overview of key linguistic transformations. Tracing the evolution from Old English to Modern English, the study emphasizes the dynamic nature of the language.

Theoretical Frameworks:

The literature review incorporates relevant theoretical frameworks. Fishman's (1972) concept of "diglossia" is applied to understand the coexistence of standard and non-standard English varieties. Moreover, Labov's (1966) theory of linguistic change contributes to the analysis of historical shifts in English language evolution.

Synthesis of Previous Research:

By synthesizing these diverse sources, it becomes evident that English language diversity is a multifaceted phenomenon shaped by historical, regional, and global influences. However, existing gaps in research highlight the need for a comprehensive study exploring the contemporary dynamics of English language diversity and its implications in the modern world. This research seeks to bridge these gaps and build upon the foundation laid by previous scholars.

Variations in English Language:

Understanding the myriad forms and variations of the English language requires a comprehensive exploration encompassing regional, socio-cultural, and historical dimensions. This section delves into the rich tapestry of English variations, shedding light on the diverse linguistic landscapes shaped by geographical, social, and temporal factors.

Regional Variations:

English, as spoken across different regions, exhibits distinctive dialects and accents. The seminal work of Wells (1982) on regional accents in the United Kingdom highlights the nuanced phonetic differences that characterize English speech within a relatively small geographic area. Further, studies by Labov (1972) in the United States underscore the influence of regionalism on lexical choices and grammatical structures.

Socio-cultural Influences:

The social context significantly shapes the way English is spoken and understood. Sociolinguistic studies by Milroy (1980) and Eckert (2000) have delved into how social factors, including class, ethnicity, and education, contribute to

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variations in English. These variations manifest not only in pronunciation and vocabulary but also in language attitudes and usage patterns.

Historical Influences:

The historical evolution of English has left an indelible mark on its variations. Tracing the linguistic journey through periods such as Old English, Middle English, and Early Modern English, as elucidated by Crystal (2005), unveils how historical events and cultural shifts have influenced vocabulary, grammar, and language structures.

Influences on English Language Diversity:

This section scrutinizes the external forces that intricately shape the diverse landscape of the English language. Examining globalization, migration, and technological advancements provides valuable insights into the dynamic interplay between these factors and the evolving nature of English.

Globalization:

The phenomenon of globalization has significantly impacted the linguistic fabric of English. Crystal (2003) posits that increased global communication has led to linguistic convergence in some aspects, while simultaneously fostering the preservation of distinct linguistic features. The influence of global media, international business, and cultural exchange contributes to the emergence of a globalized English, marked by shared vocabulary and communication norms.

Migration and Diaspora:

The movement of populations across borders contributes to the diversification of English. Investigating the works of Fishman (1972) and Clyne (1997) reveals how migration patterns lead to the creation of diasporic communities with unique linguistic characteristics. These communities not only retain elements of their native languages but also introduce novel expressions and adaptations, contributing to the richness of English language diversity.

Technological Advancements:

In the digital age, technological advancements play a pivotal role in shaping language dynamics. Warschauer (2000) and Crystal (2001) explore how technology, especially the internet and social media, acts as a catalyst for linguistic innovation and diffusion. The rapid dissemination of language through online platforms introduces new vocabulary, expressions, and communicative norms, influencing the way English is used and understood globally.

Synthesis of External Influences:

The examination of globalization, migration, and technological advancements underscores the interconnected and transformative nature of English language

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diversity. These external influences not only contribute to the emergence of new linguistic trends but also challenge traditional notions of linguistic homogeneity. Understanding the impact of these forces is essential for navigating the evolving landscape of English communication and appreciating the intricate balance between global convergence and local diversity. This exploration sets the stage for a comprehensive analysis of the multifaceted dynamics of English language evolution.

Evolution of English Language:

Tracing the historical development of English unveils a fascinating journey marked by key milestones and transformative shifts. This section endeavors to illuminate the significant epochs and linguistic transformations that have played pivotal roles in shaping the diverse landscape of the English language.

Old English Period (450-1150):

The roots of English lie in the Germanic languages spoken by early Anglo-Saxon settlers. The Old English period witnessed the infusion of Latin due to Christianization, laying the groundwork for a language with diverse influences. Key texts such as Beowulf showcase the linguistic richness of this era.

Middle English Period (1150-1500):

The Norman Conquest in 1066 introduced French influences, creating a linguistic amalgamation. Chaucer's Canterbury Tales exemplify the Middle English period, reflecting a language undergoing significant changes in vocabulary, syntax, and pronunciation.

Early Modern English Period (1500-1700):

The Renaissance era marked a surge in linguistic creativity and the standardization of English. The works of Shakespeare and the King James Bible exemplify the Early Modern English period, showcasing the emergence of a standardized form while regional dialects persisted.

Modern English Period (1700-Present):

The Industrial Revolution and colonial expansion brought English to new frontiers, fostering linguistic diversity. The standardization of English continued, with dictionaries like Samuel Johnson's and later, Noah Webster's, influencing language norms. The British Empire and later the global influence of the United States contributed to the spread of English worldwide.

Global English and Contemporary Dynamics:

The 20th century witnessed the rise of English as a global lingua franca. The advent of mass media, especially film and television, accelerated language standardization. However, English's global spread also led to regional adaptations

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and variations, with World Englishes emerging as a concept that acknowledges the diversity of English across different cultures and regions.

Synthesis of Evolutionary Transformations:

The historical journey of English reflects a continuous evolution, influenced by internal developments and external interactions. Each period contributed distinctive elements to the linguistic tapestry, resulting in the diverse and adaptable language observed today. Recognizing these historical milestones is essential for comprehending the intricate dynamics of English language diversity and its resilience in the face of evolving cultural, social, and global contexts.

Conclusion:-

In conclusion, the exploration of "Dynamics of English Language Diversity: Exploring Variations, Influences, and Evolution" has illuminated crucial facets of the complex interplay shaping the English language. Key takeaways from this study encapsulate the following:

1. Multifaceted Variations: English language diversity is intricately woven with regional, socio-cultural, and historical nuances, resulting in a rich tapestry of linguistic variations.
2. External Forces at Play: Globalization, migration, and technological advancements exert profound influences on the evolution of English, contributing to both convergence and divergence in linguistic expressions.
3. Historical Continuity: The historical trajectory of English reveals a dynamic and adaptive language, marked by transformative milestones and cultural interactions.
4. Global English: The 20th century witnessed the ascent of English as a global lingua franca, with standardization coexisting alongside regional adaptations, fostering a mosaic of World Englishes.

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CONTENTS

Chemistry

S.No.	Title	Author/s	Page No.
1	QSAR evaluation of Glucagon Receptor (GCGR) antagonists for the anti-hyperglycaemic lead development	Ajaykumar Gandhi Pooja Gaikwad Jyoti Dahatonde Archana Chapolikar	1-7
2	Synthesis and Bilogical Evaluation of Pyrazole Derivative	A P Thakare S R Kolteke	8-12
3	Healthy hydroponic cattle feed (grass) development eco-friendly & economically	Dr. Ramesh Tukaram Parihar, Dr A.G.Gaddamwar	13-18
4	Design and Synthesis of Heterocyclic Active Moieties of Pyrazoles and Its Importance's	Somwanshi A.R.	19-22
5	QSAR analysis of sodium glucose co–transporter 1 (SGLT1) inhibitors for anti-hyperglycaemic lead development	Archana Chapolikar, Jyoti Dahatonde, Pooja Gaikwad, Ajaykumar Gandhi	23-34
6	Preparation and Acetone Gas Sensing Properties of Cd Substituted Magnesium Ferrites	A. V. Kadu	35-40
7	Studies of Acoustic Properties of Substituted Chalcone in Different Percentage of Dioxane-Water Mixture	A. D. Khambre	41-44
8	Synthesis, Physicochemical evaluation of heteryl amino derivatives of bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(methylthio) pyrimidine] diazene	Girish Deshmukh Avinash Thakare, Chanda Gawande	45-49
9	Novel Synthesis and Characterization of Some Substituted Chlorosubstituted Aryl Substituted 1,3-Thiazole as Antibacterial Agents	Chhaya D. Badnakhe	50-58
10	Mini Review on biological aspects of 1,3,4-Thiadiazoles	Mr. N.D. Dahake, Dr. V.H. Masand	59-61
11	Simultaneous Non-aqueous Conductometric Investigation of Pharmaceutically Potent Ibuprofen-Paracetamol Combination Drugs	Pradip P. Deohate, Aakanksha S. Dongare Anushri R. Jalamkar	62-64
12	Cp*Co(III) Catalyzed Redox-Neutral Annulation: A Powerful Tool for Isoquinoline Synthesis from *N*-Cbz Hydrazones	Dewal S. Deshmukh Bhalchandra M. Bhanage	65-67

13	Design, synthesis, spectral characterization and anti-microbial screening of some novel 1, 2, 4-dithiazole with Coumarin moiety	K. U. Dongare S. A. Waghmare S. B. Sarkate R. N. Ingole	68-72
14	Effect Of metal-ligand complexon germination of some vegetable plants	Prof. M.M.Rathore C.N.Deshmukh	73-78
15	Preparation of Adsorbent from various natural materials for removal of heavy metal ions from waste water: Critical review	Sandhya B. Gaikwad	79-82
16	Evaluation of Antioxidant Activity by DPPH Method of Thiocarbamides	P.L. Harale M.E. Shelke D.T. Tayade	83-86
17	Investigations of Proximate Compositions of *Xanthium Strumarium L* Roots from Tisgaon (PIN Code 431002) of Taluka and District Aurangabad, India	Jawerea Nayab Mohammad Jamil Rahim Ullah Sharafat Ullah	87-89
18	Synthesis, Structural Study Of Substituted Heterocyclic Compounds	Kavita. M. Heda	90-93
19	Characterization of Diesel Mixtures by Ultrasonic Methods	K. P. Belsare N. B. Selukar	94-96
20	Phytochemical and Proximate Analysis of Leaves of *Heteropogon Contortous* (L.) Beauv	Miss Mosim Raza H. Shaikh	97-100
21	A Review of Computer-Aided Drug Discovery (CADD)	Manojkumar O. Malpani	101-105
22	Synthesis and Anti-microbial Activity of Novel 3-[(3-substitutedamino-1,2,4-thiadiaz-3-yl)]amino-5-N-TAG-amino-1,2,4-thiadiazole [11b]	M. R. Raghuvanshi	106-109
23	Sulfate promoted zirconia-based mixed oxide as solid acid catalysts for organic transformations	Sushil V. Shelke Sambhaji T. Dhumal Abhay L. Ghodke Meghshyam K. Patil	110-112
24	Structure, Physical and Chemical Properties of Thiourea with Their Derivatives	A.P. Mitake S.P. Rathod	113-119
25	Study of Proton and Metal-Ligand Stability Constants of hydroxy Substituted Chalcone Complexes pH-Metrically	Mohd. Wajid Shaikh Mohd Waris	120-123
26	Ecofriendly synthesis and characterization of Ethyl 2-imino-6-methyl-4-substituted phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate compounds	Nilesh B. Jadhav	124-126

27	Effect of Fe Dopant on Structural & Electrical Properties of Copper OxideNanoparticles	N. N. Gour A. P. Pinjarkar H. G. Wankhade P. R. Padole	127
28	Preliminary Phytochemical Studies of *Cesalpinia crista* L.	Nitin G. Asole Ramesh T. Parihar Anand S. Jadhao	128-131
29	Removal of Methylene Blue using *Cajanus Cajan* Activated Carbon	Vilayatkar N.D. Chaudhari D.L. Kadu N.S. Kurzekar R.R.	132-134
30	Conductometric Studies of [CPHDD] and [CTMBCD] at Different Molar Concentrations and Different Percentage Compositions in Water-Ethanol Mixture	K.P. Jumde Sanghapal S. Padhen Saleem R. Khan D.T.Tayade	135-140
31	Synthesis and Characterization of Some Substituted Chalcone by the Green Synthesis Way (Grinding Method)	Nilesh S. Padole Murlidhar P. Wadekar Shubhangi Y. Deshmukh Vinod M. Sherekar	141-144
32	In-Silico Prediction of Phytoconstituents From Solanum Indicum for Antiepileptic Activity	Pooja.P.Patle Parimal Katolkar Pradeep Raghatate Jagdish Baheti	145-156
33	Deep Discoveries in Chemistry: Unraveling the Mysteries at the Molecular Level	Dr. Prashant R. Mahalle	157-159
34	Synthesis, Characterization of (3-Chloro-benzylidene) – **(**4-Phenyl-thiazol-2-yl**)** amine and Studied their antioxidant Activity	Ghodile R.D Chaudhari P.S. Dharamkar R. R	160-164
35	Synthesis and Characterization of Schiff Bases Using Different Amines and their Biological Activities	Priyadarshani N Deshmukh	165-167
36	Physico-Chemical Assessment of Soil Sample in Jarud Region in Amravati District of Maharashtra (India)	Dr. Priyanka U. Belsare Ku Tejashri M. Ghotkar	168-171
37	Synthesis ,Characterization And Antimicrobial Study Of Co(II),Cu(II) and Fe(III) Complexes Of Substituted 4,4'-Dimethoxybenzoinhydrazones	P. M. Dahikar	172-175
38	Study of Extraction and Chemical Screening of *T. cordifolia* (Guduchi) Stem & Leaves	Ramesh Tukaram Parihar S A Quazi Shaikh Farah T	176-178

39	In-silico QSAR-based virtual screening recognition of novel anaphylactic lymphoma kinase inhibitor	Rahul D. Jawarkar Praveen Sharma Sachin Kumar Jain	179-196
40	Synthesis, characterization and biocidal study of some novel 2-hydroxy 4,6-disubstituted phenyl pyrimidines bearing 4-bromo phenol moiety	Rajendra M. Pathade Pravin. S. Bodkhe	197-203
41	Investigation of antimicrobial Activities of Dihydropyrazines	Manish Fukate Sheryil Malvilayils Roshan Jaiswal Swati Bawiskar	204-208
42	Synthesis and Spectral Characterization of Novel 1,2,4-Dithiazole Derivatives	Mr Ramdas N Ingole Dr Siddharth S Waghmare Dr Pravin S Bodkhe	209-211
43	Synthesis of Substituted Flavanones and their Impact on Seed Germinations	S. P. Rathod R.T.Parihar A.P.Mitake T.M.Bhagat S. B. Waghmare	212-215
44	Antimicrobial Resistance : A Global Challenge	Reshal Deshmukh	216-217
45	Wings across Reservoirs: Understanding and Safeguarding the Migration Patterns of Insectivorous Birds in Anthropogenic Landscapes	Dr. Chandrashekhar R. Kasar Ku. Revati Kishor Lonkar	218-222
46	Synthesis and Characterization of Pyrazolone and its derivatives	Mr. R. N. Gaikwad	223-225
47	Preliminary Phytochemical analysis of Leaves extract of the plant *Justicia Adhatoda*	Swapnil D. Bhagat Sopan D. Ingole Varun A. Mahale Nandkishor S. Thakare Chandrakant U. Dhanwad	226-229
48	*In-Silico* Prediction of Phytoconstituents From *Solanum Indicum* for Antistress Activity Targeting Ask 1 Inhibitor	Sakshi Mude Parimala Katolkar Pradeep Raghatate Jagdish Baheti	230-241
49	Design, Synthesis, Spectral Characterisation and Antibacterial Screening of Some Novel 4-Substitutedimino-1,3,5-Dithiazine Along With Pyrimidine Nucleus	S. B. Sarkate[a] S. A. Waghmare K. U. Dongare R. N. Ingole	242-245
50	Comparative Account of Partial Molar Volumes and Compressibilities of Aqueous-(L-Arginine + Glucose/Lactose) Solutions at 310.15 K	R. V. Dudhate H. N. Pawar B. R. Bhosle S. D. Deosarkar S. D. Deshmukh P. S. Bodkhe	246-249

51	Studies in the Synthesis of 5-(3-Substitutedthiocarbamido) Aminoindole by Microwave Technique	M. B. Shahakar R.D. Isankar P.V. Raut	250-254
52	Understanding the Role of Lipophilicity and Pharmacophore Elements in Pyrimidinedione based BCAT1 Inhibitory Activity	S. R. Deshmukh P.P. Nalawade V. H. Masand S. D. Thakur P. S. Navale	255-258
53	Use of Formic Acid as Co Surrogates in Palladium Catalyzed Carbonylation Reaction	Shoeb R. Khan Pratik E. P. Michael Mayur V. Khedkar	259-264
54	*In-Silico* Prediction of Phytoconstituents From *Solanum Indicum* for Antianxiety Activity	Shweta Dhole Parimal Katolkar Pradeep Raghatate Jagdish Baheti	265-275
55	Computational Insight on the Argentophilic Interactions of Axially Chiral Ag-NHC Complex of *R*-BINOL Scaffold via TD-DFT	Sonali Ramgopal Mahule	276-279
56	Agricultural Influence and application of Mn(III), Fe(III) and VO(IV) Schiff base metal Complexes	S. R. Kelode	280-283
57	Recent Applications of Deep Eutectic Solvent (DES), a Greener Media in Organic Synthesis	Suchita B. Wankhede	284-290
58	Synthesis, Characterization and Pharmacological Evaluation of Some New Functionalized Flavone Derivatives From B-Diketones	Sushil K. Pagariya Pravin S. Bodkhe	291-297
59	Design, Synthesis, Spectral Characterisation and Antibacterial Screening of Some Novel 4-Substitutedimino-1,3,5-Dithiazine Along With Pyrimidine Nucleus	S. B. Sarkate S. A. Waghmare K. U. Dongare R. N. Ingole	298-302
60	Colorimetric Phytochemical Analysis of Tinospora Cordifolia and FTIR Study of Its Medicinal Sample Giloy Ghanvati	Dr Swaroopa Rani N. Gupta	303-317
61	Determination of Hydochloric Acid Neutralizing Capacity of Different Antacid Tablet by Back Titration Method and Its FTIR Analysis	Dr Swaroopa Rani N. Gupta	318-328
62	Investigation of Physico-chemical parameters of groundwater from Barshitakli tehsil region, Akola district, Maharashtra, India	Dr. S. S Deshmukh Dr. Tejas R. Patil	329-332

63	Identification of confluence of multiple scaffolds required for Aurora Kinase A inhibition	Vijay H. Masand S.D. Thakur M.M. Rathore	333-335
64	Synthesis, Characterization and Biological Evaluation of 4-(4-Bromo-1-Hydroxy Naphthalen-2-Yl)-6-(4-Hydroxy Phenyl)-5,6-Dihydropyrimidine-2(1h)-One	Dr. V. M. Sherekar Mr. Nilesh S. Padole	336-339
65	Efficient Synthesis of Salicylaldehyde-Based Schiff Bases Using Hydrothermal Sonication: A Green Approach	Vivek Ramkrushna Mate Datta Anandrao Patil Kalpana B. Gawande Sanjay R. Thakare Rajkumar Uddhavrao Pokalwal	340-345
66	Viscometric Technique for Evaluation of 1-Phenyl-3-[4-(2-Ethylimino-4-T-Butylimino-1,3,5-Dithiazino)Amino- Phenyl]Prop-2-Ene-1-One in Ethanol-Water Mixture	S.S. Padhen A.B. Wadekar	346-348
67	An Overview on Green Chemistry	Dr. Rupali.S. Talegaonkar	349-353
68	3D Printing Technology for development of Transdermal Drug Delivery Systems	Dr. Amar Deshpande Dr. Jagdish Baheti	354-358
69	*In-silico* Prediction of Phytoconstituents from *Hymenodictyon excelsum* for Antimalarial Activity Targeting Hypoxanthine-guanine phosphoribosyltransferase (HPRT1)	Parimal Katolkar Jagdish Baheti	359-372
70	Spectrophotometric Complexation Study of Cu(II) with 8-Hydroxyquinoline based Azo dye	Santosh M. Chavan Nilesh V. Rathod Manoj S. More Chandrakant D. Ghugare Ravi E. Khadse Jayshri S. Jadhao Akash V. Kubade Parikshit S. Thakare	373-377
71	A Comprehensive Review on Various Method of Synthesis and Biological Activities of Schiff Bases with Heterocyclic Moiety	Rahul P. Rahate	378-383
72	Revolutionizing Applications: A Comprehensive Review of Schiff Base Nanoparticles at the Nanoscopic Scale	S. R. Khandekar	384-389
73	Screening Of Antioxidant Property Present In Psidium Guajava Linn	V D Mane P P Mhasal	390-394

74	In-Silico Prediction of Phytoconstituents From Solanum Indicum for Antiepileptic Activity	Pooja P. Patle Parimal Katolkar Pradeep Raghatate Jagdish Baheti	395-405
75	Development and Characterization of Piroxicam Matrix Based Transdermal Patch	Pragati Hasbe Zohra Firdous M.S.A Pankaj Dhapke Jagdish Baheti	406-410
76	Analytical Method Development and Validation of Antidiabetic Drugs	Prajakta Sontakke Disha Dhabarde Jagdish Baheti	411-414
77	Synthesis of colloidal metal oxide using reverse micelle technique and its application in coupling reactions for Benzoxazole formation	Ramesh N. Zade Pravin S. Bodakhe Kishor B. Raulkar Bhupesh M. Mude	415-418
78	Synthesis, Charecterization and Biological Evaluation of Coumarin – Chalcone Derivatives	Disha M. Dhabarde Punam B. Rathi Ashish Telrandhe	419-420
79	Synthesis and Characterization of (3-(3,5-dichloro-2-hydroxyphenyl)-5-(pyridin-2-yl) isoxazol -4-yl)(phenyl) methanone with microwave irradiation	P. S. Nandurkar M. M Rathore	451-424
80	Microbial Examination of Nanoparticle of Tetra-O-acetyl-B-D-Glucosyl-5aryl-4-Dithiobiurets	Ashish G. Sarap P.T. Agrawal	425-428
81	Synthesized PANI/Cu-NPs / Aloe-Vera thin films Biocomposites for ammine gas sensor stimulator	Dr. D. B. Dupare	429-435
82	Structural and Ion-Exchange Properties of Copolymer Derived from 4, 4'-Biphenol - Benzidine – Formaldehyde	P. P. Kalbende M. S. Dhore S. S. Butoliya	436-445
83	Navigating the Therapeutic Landscape: Discovery and Pharmacophore Modeling of BRD4 Inhibitors for Prostate Cancer Precision Treatment	Mr. P S. Nawale Ms. A D. Mehakare Dr. J R. Bansod Prof. Capt. M M. Rathore	446-451
84	Synthesis and Characterization of Novel Activated Carbons derived from different parts of Abutilon Indicum plant by using $ZnCl_2$ activating agent	Farooque Haider Zulfequar Haider Gunwant Hari Kurhade	452-456
85	A Review Study on pyrazole containing flavones by using Green Solvents	Shaikh A.Baseer	457-460
86	A Review of Supramolecular Chemistry: Unlocking a Promising Future	Prasanna S Pande	461-462

87	Antimicrobial Screening Of Schiff Base (E)-N1-((5-Methylfuran-2-Yl) Methylene)-5-Nitrobenzene-1,2-Diamine Against E. Coli	G. D. Rawate D. A. Pund	463-464
88	Effect of Fe Dopant on Structural & Electrical Properties of Copper Oxide Nanoparticles	N.N.Gour A.P.Pinjarkar H.G.Wankhade P.R.Padole	465-468
89	Synthesis, Characterization of (3-Chloro-benzylidene) – (4-Phenyl-thiazol-2-yl) amine and Studied their antioxidant Activity	Ghodile R.D Chaudhari P.S. Dharamkar R. R	469-472
90	A Review: An Overview on Studies of Stability Constant of Metal Ions with Substituted Pyrazoles p^H-Metrically	C. M. Shahakar V. S. Jagtap N.S.Padole P.B.Rathod	473-481
91	Synthesis of (E)-3-(5-chloro-2-hydroxyphenyl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)prop-2-en-1-one And Their Oxazine and Thizine derivatives.	B.G.Maske R.R.Wankhade	482-484
92	Structural Elucidation of Synthesized Substituted 1,3,4-Thiadiazole Molecules through Pharmacophore Modelling	C. N. Jadhav M. M. Rathore V. H. MAsand K. S. Shelki	485-494
93	Photocatalytic activity of Niobia-hematite Nanocomposites Synthesized by Sol-gel Method	M.J. Pawar M. M. Rathore A.D. Khajone K.A. Pawar	495-501
94	Pharmacophore Analysis of Substituted 1,3,4-Thiadiazole Derivatives: Unravelling Structural Insights for Enhanced Antibacterial Activity	Tauheed Nadeem M. M. Rathore V. H. MAsand C. N. Jadhav	502-507
95	Exploring the Binding Affinity of N-Phenylbenzamide Derivative Using Pharmacophore Models in T. Brucei Parasites.	Jayant R. Bansod Sanjay P. Mote Prashant S. Nawale	508-512
96	Continuous Fixed Bed Adsorption of Heavy Metals Removal Using Granular Activated Carbon	Dr.V.R.Kinhikar	513-515
97	Sustainable Production and Analysis of Silver Nanoparticles Using Extract from Portulaca oleracea Leaves for Eco-Friendly Applications	Pradnya Nalawade	516-518
98	Studies in the Synthesis of 5-(3-Substitutedthiocarbamido) Aminoindole by Microwave Technique	M. B. Shahakar R.D. Isankar P.V. Raut	519-522

99	Study of Physico-chemical Parameter of Soil Analysis in Buldhana district	Wagh P.B. A. D. Deshpande G. B. Andhale	523-526
100	Formulation and Evaluation of Chitosan Nanoparticle Based *In-Situ* Nasal Gel For Parkinson's Disease	Ms.Vaishnavi Ghati Mr. Kiran A. Tengse Dr. Pankaj Dhapke Dr.Jagdish Baheti	527-535
101	Synthesis and characterization of 2-[2-amino-6-(3,4-substitutedphenyl)-6H-1,3-oxazin-4-yl]-4-chloro-3-substituted phenol with special reference to their antioxidant activity	B.P.Khobragade S.E. Bhandarkar	536-538
102	Structural Characterization of Sulfur Nanoparticles Synthesized by Biowaste Orange Peels Extract via Herbal Method	S.G. Khobragade N.S. Dixit M.S. Dixit D.A. Pund A.S. Dixit	539-541
103	Thermal Decomposition Kinetics of Cr(III), Mn(III), Fe(III), VO(IV) and UO_2(VI) Schiff Base complexes	P. R. Mandlik P. R. Deshmukh P. K. Deshmukh	542-545
104	A Comparative Analysis of Molecular Docking: Mono Versus BisDerivatives of Isoniazid	Payal K Kadu D S Ghorpade J M Barabde	546-549
105	Eco-Friendly Synthesis and Characterizaton New Chalcone Derivatives	Shubhangi Y. Deshmukh Mithilesh M. Rathore Nilesh S Padole Mamta A. Choudhary	550-552
106	Synthesis and Application of Sorbitol Based polymers and their cleaning capacity	Anand D.Deshpande Pradip B. Wagh	553-556

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Chemistry

1

QSAR evaluation of Glucagon Receptor (GCGR) antagonists for the anti-hyperglycaemic lead development

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ABSTRACT: GA-MLR **based** QSAR evaluation has been effectuated on a small dataset of GCGR antagonists abide by OECD principles. Present study t revealed some of the structural features such as minimum possible occurrence of -H_2CCH-, $PhCH_2$- moieties and more number of carbon atoms at topological distance of 10 from halogen(s) as crucial for better GCGR antagonistic activity. Developed QSAR model performed very well for all the approved statistical parameters such as, $R^2 = 0.90$, $Q^2_{LOO} = 0.87$, $Q^2_{LMO} = 0.82$, $Q^2F^n = 0.86–0.92$, $CCC_{ext} = 0.93$. Applicability domain analysis and Y-randomization test also enhanced the credibility of this study.

KEYWORDS: QSAR, GCGR, hyperglycaemia

ABBREVIATIONS:

CADD- Computer **A**ided **D**rug **D**esigning, **GCGR- G**lu**ca**g**o**n **R**eceptor, **GCGRA- G**lu**ca**g**o**n **R**eceptor **A**ntagonist, **SMILES- S**implified **M**olecular-**I**nput **L**ine-**E**ntry **S**ystem, **GA- G**enetic **A**lgorithm, **MLR- M**ultiple **L**inear **R**egression, **QSAR- Q**uantitative **S**tructure-**A**ctivity **R**elationship, **QSARINS**-QSAR Insubria, **OECD- O**rganization for **E**conomic **C**o-operation and **D**evelopment, **OFS- O**bjective **F**eature **S**election, **SFS- S**ubjective **F**eature **S**election

1. INTRODUCTION

A lifestyle induced metabolic disorder, Type 2 Diabetes Mellitus (T2DM) is the prevalent and ever escalating type of the diabetes, worldwide. To date, **463** million people have diabetes and an estimated global projection for diabetes is 578 million adults by 2030[1]. Cardiovascular discomfort, retinopathy, nephropathy are some of the health complications that are consequences of hyperglycaemia. Glucagon – a peptide hormone, known to elevate hepatic glucose production by stimulating gluconeogenesis and glycogenolysis and regulates blood glucose homeostasis collaboratively with insulin. In both, type 1 and type 2 diabetes, increase in glucagon level and/or insufficient glucagon suppression contribute to the hyperglycaemia. Glucagon Receptor (GCGR) antagonism emerged as a promising therapy to control hyperglycaemia. BAY 27-9955 was the first clinically approved GCGR antagonist. MK-357732, MK-0893, PF-06291874, LY- 2409021, and LGD-6972 under trial GCGR antagonist[2]–[5]. GCGR is a well-established target for glucagon suppression and hence further optimization of reported compounds may possibly suffice a better lead of desired anti-hyperglycemic potency with minimum and less serious side effects

Computer Aided Drug Designing (CADD)[6]–[8] being result oriented, time- and cost-efficient, and eco-friendly approach, is now an established drug discovery approach. QSAR–is a multidisciplinary approach wherein experimentally determined bio-activity of molecule is statistico-mathematically correlated to its molecular features (expository QSAR) which further assist in an *in silico* bio-activity prediction (statistical QSAR)[9]–[11]. Expository QSAR intelligibly aligned with statistical QSAR provides better insights for the pharmacokinetics[12]–[19].

In the recent work, a QSAR model using dataset of 44 GCGRAs with experimentally determined GCGR binding activity is developed. Decidedly this model will assist synthetic organic chemists in the development of better GCGRA as anti-hyperglycemic lead.

2. MATERIALS AND METHODS

A. *Selection of data-set*:

A dataset of 44 Glucagon Receptor Antagonists (GCGRAs) with *in vitro* GCGR binding activity in terms of half-maximal inhibitory concentration (IC_{50}) ranging from 0.02 to 131.1 μM (converted to pIC_{50}) is used[20], [21]. The variation in GCGR binding activity with chemical features, illustrated using five least and five most active compouds (**Figure. 1**). The SMILES strings with reported IC_{50} and pIC_{50} values for all the GCGRAs are present in the Table S1 in the supplementary material. (A google drive for supplimentary information provided at the end)

B. *Molecular Structure Drawing and Optimization:*

Free and open source software, ChemSketch 12 Freeware (www.acdlabs.com) is used to draw 2D structures and further conversion to 3D structures is achieved using OpenBabel 2.4.0. A geometry optimized molecule is characterized by its lowest energy i.e. most stable conformation. Geometry optimization ensures the normalization of all such a physico-chemical properties for all the molecules from dataset and makes it a necessarily important step prior to molecular descriptor calculation. As a step forward, force field MMFF94 available in TINKER is used for optimization of the molecules.

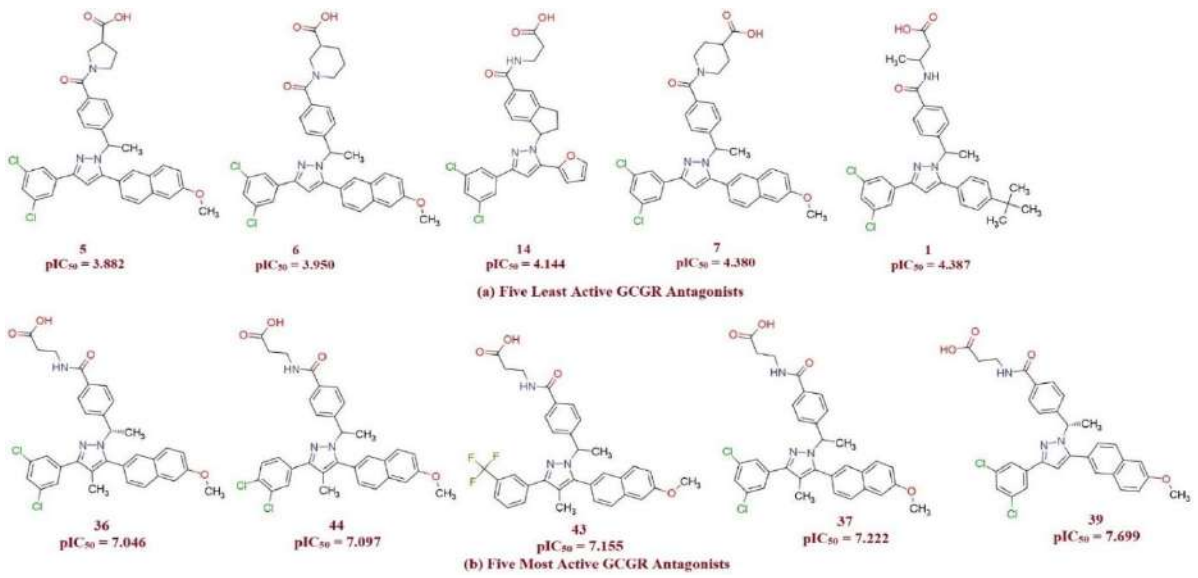


Figure 1: Variations in activity and chemical structure in the present dataset of GCGRAs (a) five least active compounds (b) five most active compounds.

C. *Molecular Descriptor Calculation and Objective Feature Selection (OFS):*

A molecular descriptor is a structural and physico-chemical property of a molecule or specific part of the molecule. More than 18,000 molecular descriptors were calculated for each molecule using PyDescriptor[22] and PaDEL[23]. In the data pruining step, Objective Feature Selection (OFS) in QSARINS v2.2.4[24], [25] screened out multi-collinear and spurious molecular descriptors (i.e. with nearly constant values >95%, co-linearity |R| >0.95) and contracted molecular descriptor pool with 1145 variables is generated. Contracted though, molecular descriptor pool has covered adequately comprehensive chemical space being comprised of 0D– to 3D– descriptors, structural, constutional properties and charge descriptors etc.

D. *Subjective Feature Selection, QSAR Model – Development and Validation:*

In accordance with the OECD principles, firstly, apt variable selection method GA– MLR[26] in Subjective Feature Selection (SFS) operation in QSARINS v2.2.4 is used to perform simple and easy to interpret QSAR models. Then, all the derived models were subjected to the thorough

statistical validation, Y-scrambling and Applicability Domain analysis. The steps in QSAR building process:

I. Random split operation in QSARINS v2.2.4 split given dataset into a training set with 35 molecules (80%) and a prediction set with 9 molecules (20%) prediction. Molecules in training set were utilized for QSAR model development and external validation was performed on 9 molecules in prediction set.

II. QSAR models were built using Subjective Feature Selection (SFS) operation in QSARINS v2.2.4 (at default settings) by setting Q^2_{LOO} as fitness function. Insignificant increase in Q^2_{LOO} value was observed after 5 variables and hence to avoid overfitting SFS opertion is confined to 5 variables which additionally helped in deriving easy and informative QSAR models. (See supplementary information Table S2)

III. (a) Leave-One-Out (LOO) and Leave-Many-Out (LMO) parameter based internal validation; (b) External validation; (c) Y-scrambling and model Applicability Domain (AD) analysis, performed for legitimate validation.

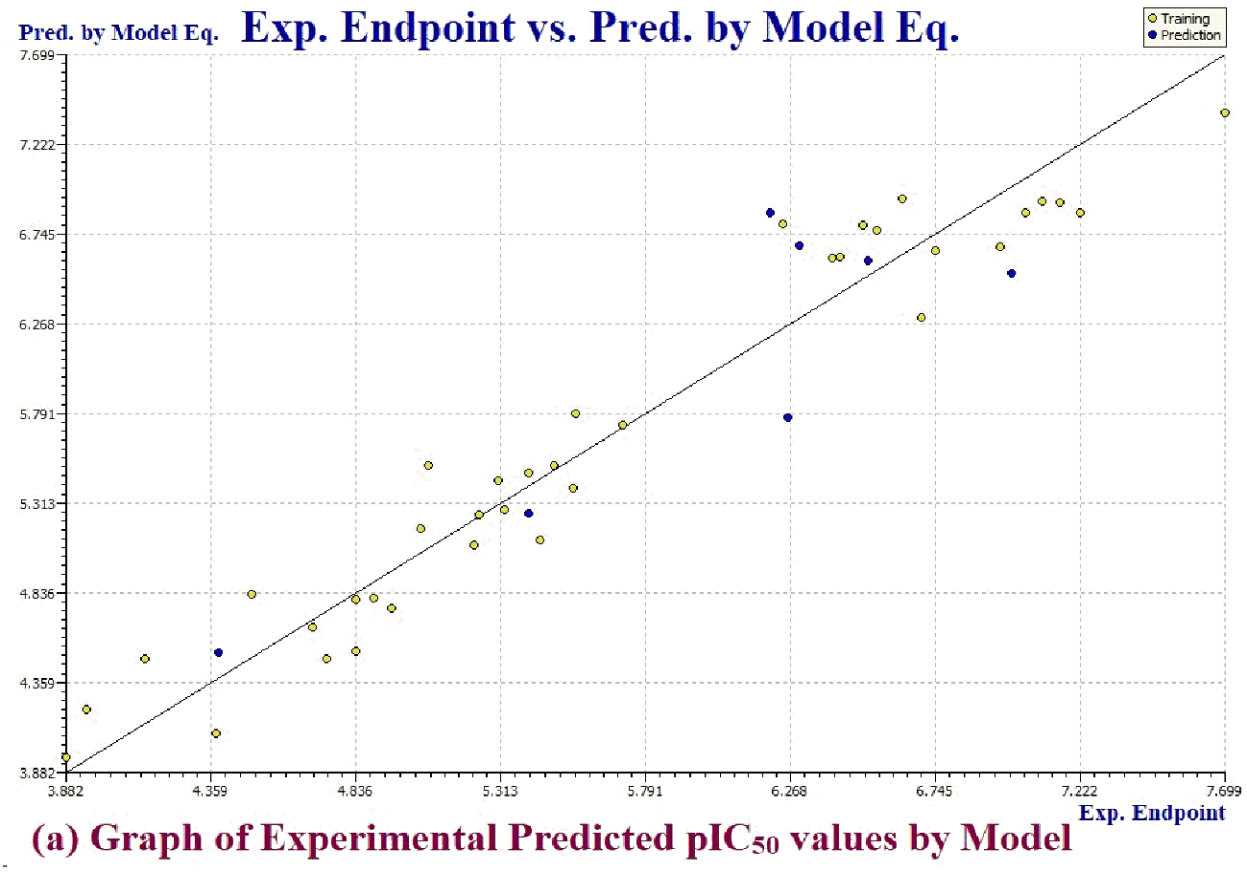
IV. Performance of each model, measured by close inspection of the various statistical parameters meter the robustness of the GA-MLR based QSAR model. The QSAR model with best values of these parameters and with best predicative ability is selected.

3. RESULTS

- Values of Fitting, Internal Validation, and External Validation are very well above the approved threshold values.
- The predictiveness of the generated QSAR model can be corroborated from **Figure 2a**.
- Moreover, Model applicability domain (AD) of the model is corroborated from Williams plot (Figure.2b).
- **QSAR Model** (Divided Set: Training Set-80% and Prediction Set-20%):
  pIC_{50} = 7.941(±1.078) - 0.148(±0.068)***H_don_8B*** - 1.594(±0.204)***KRFPC298*** - 1.700(±0.490) ***KRFPC582*** + 0.106(±0.047) ***APC2D10_C_X***

  [R^2 = 0.90, R^2_{adj} = 0.88, Q^2_{LOO} = 0.87, Q^2_{LMO} = 0.82, RMSEtr = 0.25, MAE_{tr} = 0.25, RSS_{tr} = 3.86, CCC_{tr} = 0.95, s = 0.35, F = 70.22, $RMSE_{cv}$ = 0.36 MAEcv = 0.29, $PRESS_{cv}$ = 4.80, CCCcv = 0.93, R2ext = 0.90, Q2-F1 = 0.88, Q2-F2 = 0.86, Q2-F3 = 0.92, CCCext = 0.93]

- Compounds 13, 40, 22, 17 and 16 with Predicted Models Equation Residual values in the range –0.012 to +0.032 are best predicted for their GCGR activity (pIC_{50}) in the present QSAR evaluation (Figure. 3).
- All these five compounds fall within Applicability Domain, as evident from William Plots (Figure. 2b). On the other hand, GCGR binding activity of Compound 31 is worst predicted for by the QSAR models and turned out as an outlier.



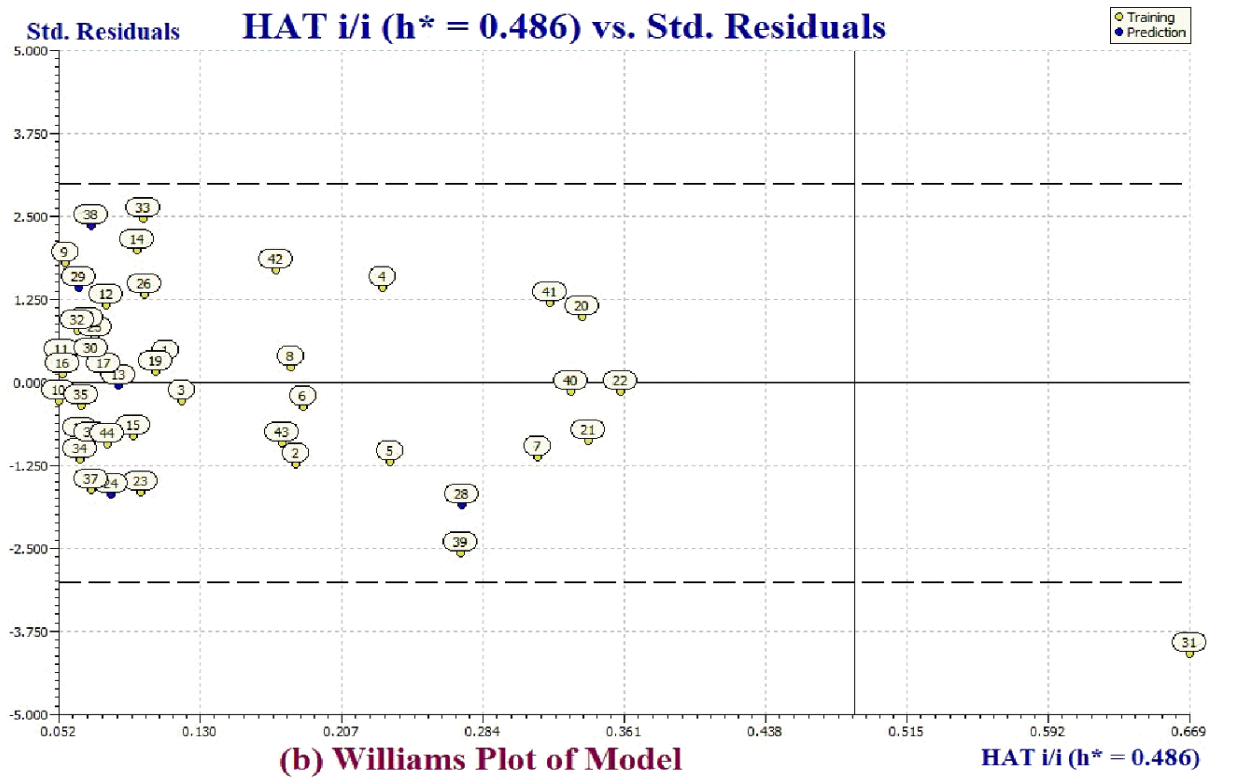


Figure 2: For QSAR Model (a) Graph of Experimental vs. Predicted pIC50 values (b) Williams plot.

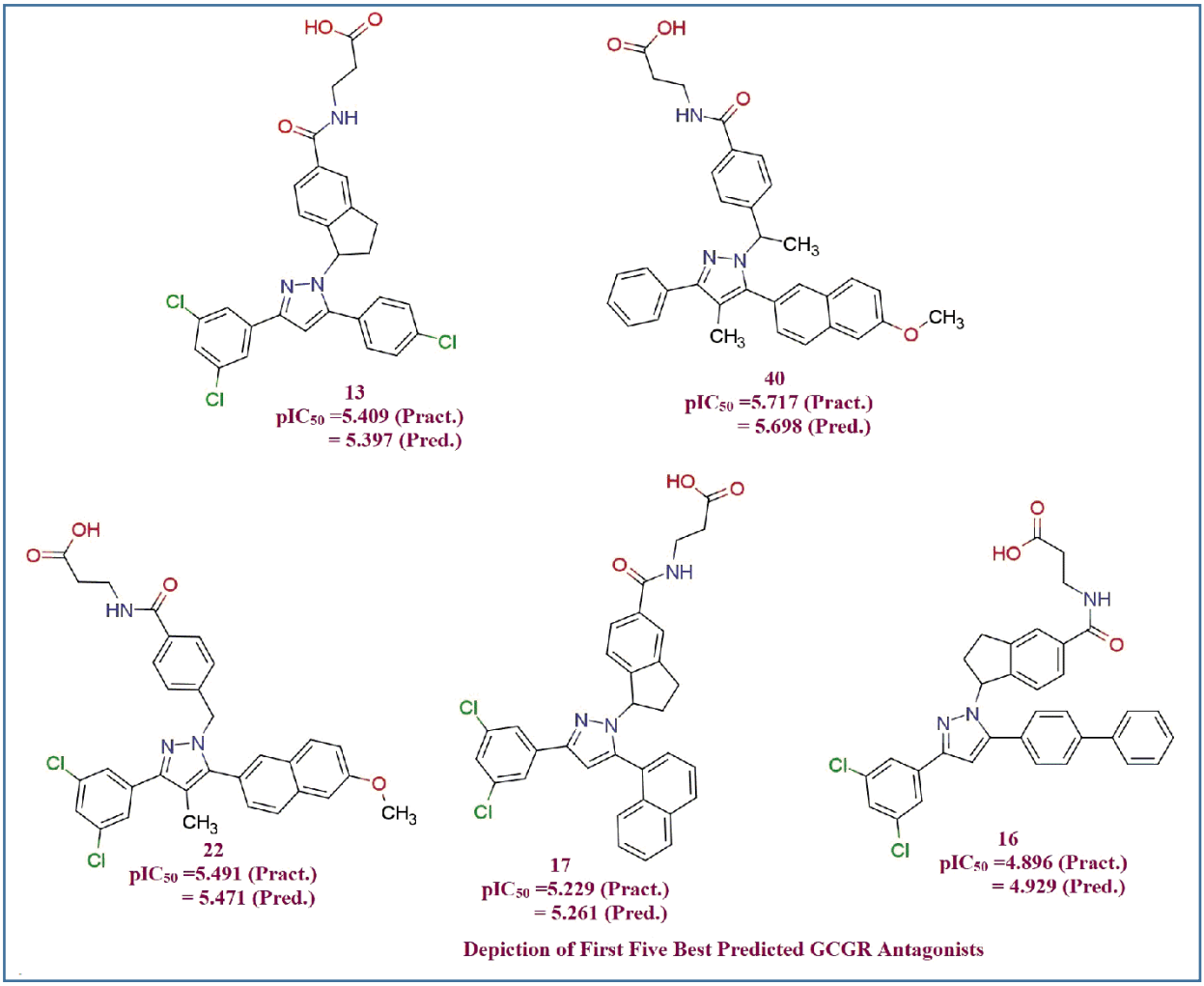


Figure 3: Depiction of first 5 Best Predicted Molecules

4. DISCUSSION

- *H_don_8B (-VE correlation with GCGR binding potency)* small possible number of *Hydrogen atoms within 8 bonds from HBD atom* is advisable for more potent GCGR antagonist
- *KRFPC298* and of *KRFPC582 8B (-VE correlation with GCGR binding potency)* less frequent occurrence of H_2C-CH and of $PhCH_2$- structural fragments, respectively are recommended for better GCGR binding potency.
- APC2D10_C_X *(+VE correlation with GCGR binding potency)* more frequent occurrence of Carbon at topological distance of 10 from any halogen is advocated by QSAR evaluation

5. CONCLUSIONS

Decidedly, a QSAR evaluation of a given series of compounds revealed some prominent structural/chemical traits that are responsible for the enhanced activity of the compound, such as minimum occurrence of $-H_2CCH-$ and $PhCH_2$- structural fragments, and less possible number of hydrogen atoms within eight bonds from hydrogen bond donor atoms, and more number of Carbons at topological distance of ten from halogen(s) which revealed the scope for optimization of the lead for better GCGR binding potency. The QSAR model will assist in optimizing leads to better GCGR binding potency to curb hyperglycaemia and diabetes.

ACKNOWLEDGMENTS: The authors are thankful to Dr. Paola Gramatica and her team for providing QSARINS-v2.2.4 and developers of TINKER, ChemSketch 12 Freeware (ACD labs), and PyDescriptor for providing the free versions of their software.

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2

Synthesis and Bilogical Evaluation of Pyrazole Derivative

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Abstract:

Pyrazole, a five-membered heterocycle containing two nitrogen atoms, is extensively found as a core framework in a huge library of heterocyclic compounds that envelops promising agro-chemical, fluorescent and biological potencies. Attributed to its several potential applications, there is a rise in the significance of designing new pyrazoles. The current study presents the synthesis of pyrazole derivatives by the reaction of chalcones with aryl hydrazine hydrochlorides in acetic acid (30%) under reflux conditions in good yields. Structures of synthesized new pyrazoles were confirmed by spectral studies.
Biological activity of all the synthesized compounds was checked against gram positive and gram negative bacteria. It has been found that all compounds shows good antimicrobial activity.

Introduction:

Heterocyclic compounds are a highly valuable and unique class of compounds. These compounds demonstrate a broad spectrum of physical, chemical and biological characteristics. Amongst heterocyclic compounds, nitrogen-containing heterocycles are extensively found as a core framework in a huge library of heterocycles and show several employments in natural science and other areas of science. Additionally, nitrogen-containing heterocycles have striking structural features and they are widely observed in natural products, for instance, vitamins, hormones and alkaloids.

Chalcones are the principal precursors for the synthesis of bioactive small molecules such as benzothiazepines, pyrazolines, isoxazolines, cylopropanes, oxadiazoles, etc., The chalcones are most commonly synthesized via Claisen-Schmidt reaction of an aromatic aldehyde with acetophenones. Chalcones has gained importance due to their simple structures and diverse pharmacological applications. Design and synthesis of simple heterocycles with various bioactivities is a worthwhile contribution in organic synthesis. The compounds with thiophene are the most important class in active pharmaceutical drugs and remain the choice for anti-inflammatory agents in spite of multiple attempts at exploring alternative scaffolds. [1-5]

II. EXPERIMENTAL

All melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on KBr disc using Perkin Elmer-1800 intrachord. ^{1}HNMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Brucker Avance 400MHz spectrophotometer with TMS as internal standard (chemical shifts are expressed in δ ppm). The mass spectra were recorded on a Joel SX-102 (EI/CI/FAB) mass spectrometer at 70 eV. The reactions were monitored by the TLC on silica gel G plates in the solvent system benzene–methanol mixture (9:1). All reagents were purchased from commercial suppliers and used without further purification. The compound includes 2-hydroxy-4-methylacetophenone, benzaldehyde, p-chloro benzaldehyde, anisaldehyde, 4-methyl benzaldehyde.

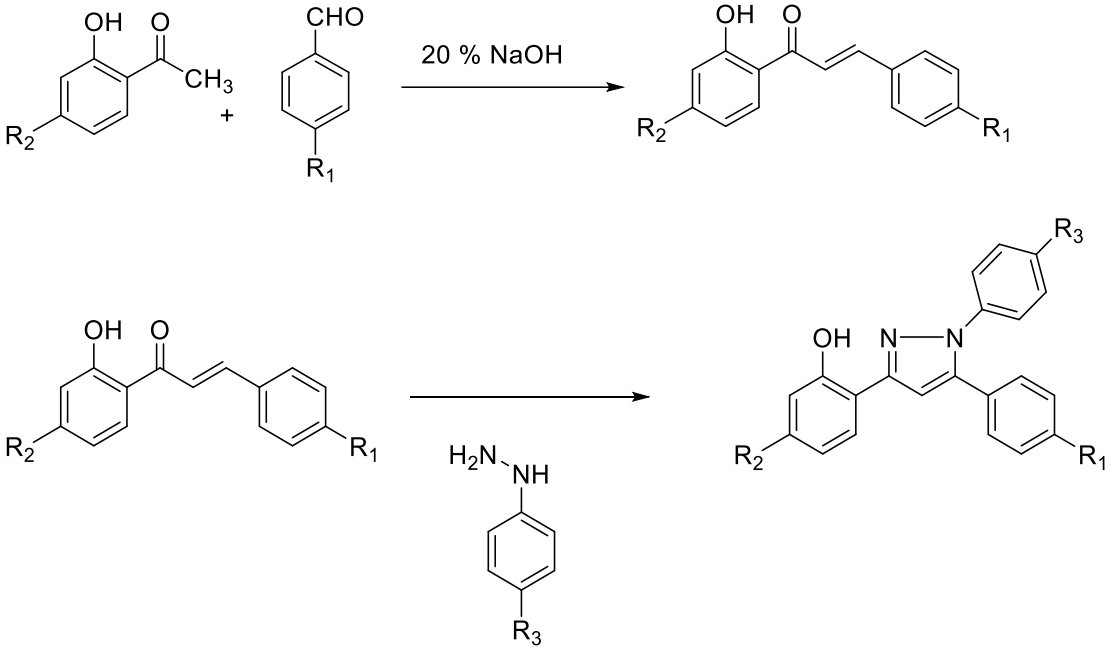
Synthesis of chalcone:

A mixture of 0.01 mol 2-hydroxy-4- methylacetophenone and 0.01 mol various aldehyde added into ethanol solvent. To this reaction mixture 20 % NaOH added and heated for several minutes

upto formation of solid residue. By keeping overnight residue nuetralized by ice cold HCl solution, filtered and dried in oven.

Synthesis of Pyrazole:

A mixture of synthesized chalcone and aryl hydrazine hydrochloride in aqueous acetic acid under reflux condition produced pyrazole derivative.



Result & Discussion:

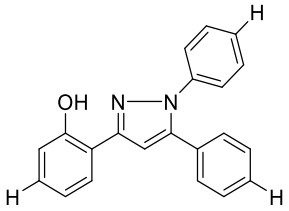
Sr No	Compounds	R_1	R_2	R_3
1	2-(1,5-diphenyl-1H-pyrazol-3-yl)phenol	H	H	H
2	2-(1-phenyl-5-(p-tolyl)-1H-pyrazol-3-yl)phenol	CH_3	H	H
3	2-(5-(4-chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)phenol	Cl	H	H
4	2-(5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)phenol	OMe	H	H
5	2-(5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)-5-methylphenol	OMe	CH_3	H
6	2-(5-(4-chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)-5-methylphenol	Cl	CH_3	H
7	5-methyl-2-(1-phenyl-5-(p-tolyl)-1H-pyrazol-3-yl)phenol	CH_3	CH_3	H

Table: Analytical Data of Synthesized Compounds

Sr No	Molecular formula	M.P. (°C)	Yield (%)	C %	H %	N %
1	$C_{21}H_{16}N_2O$	112	84	80.75	5.16	8.97

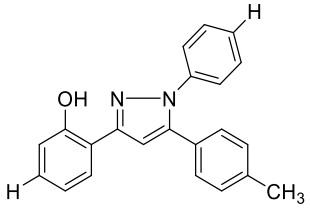
2	$C_{22}H_{18}N_2O$	119	78	80.96	5.56	8.58
3	$C_{21}H_{15}ClN_2O$	110	76	72.73	4.36	8.08
4	$C_{22}H_{18}N_2O_2$	123	81	77.17	5.30	8.18
5	$C_{23}H_{20}N_2O_2$	121	84	77.51	5.66	7.86
6	$C_{22}H_{17}ClN_2O$	120	80	73.23	4.75	7.76
7	$C_{23}H_{20}N_2O$	105	88	81.15	5.92	8.23

1) 2-(1,5-diphenyl-1H-pyrazol-3-yl)phenol



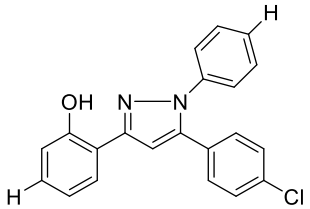
IR (KBr) *v*: 3059(Ar C-H), 3345 (O-H), 1330 (C-N), 1226 (C-O).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.05 (s, 1H, OH), 7- 8.26 (m, 14H, Ar)

2) 2-(1-phenyl-5-(p-tolyl)-1H-pyrazol-3-yl)phenol



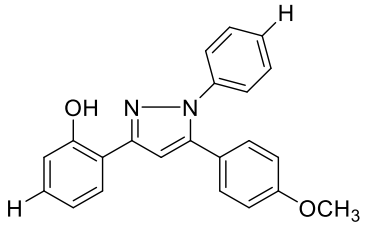
IR (KBr) *v*: 3059(Ar C-H), 3345 (O-H), 2990 (aliphatic C-H), 1328 (C-N), 1226 (C-O).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.05 (s, 1H, OH), 7- 8.26 (m, 13H, Ar), 2.34 (s, 3H, CH_3)

3) 2-(5-(4-chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)phenol



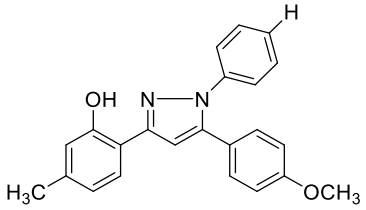
IR (KBr) *v*: 3059(Ar C-H), 3345 (O-H), 2990 (aliphatic C-H), 1328 (C-N), 1226 (C-O).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.02 (s, 1H, OH), 7- 8.26 (m, 13H, Ar)

4) 2-(5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)phenol



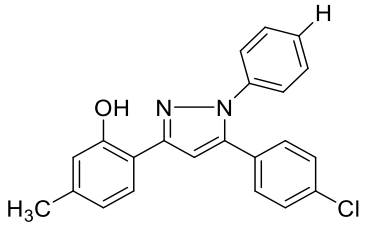
IR (KBr) *v*: 3059(Ar C-H), 3345 (O-H), 2990 (aliphatic C-H), 1328 (C-N), 1226 (C-O).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.02 (s, 1H, OH), 7- 8.26 (m, 13H, Ar), 3.81 (s, 3H, OCH_3)

5) 2-(5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)-5-methylphenol



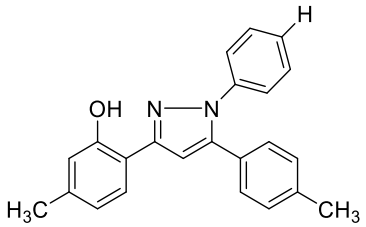
IR (KBr) *v*: 3059(Ar C-H), 3345 (O-H), 2990 (aliphatic C-H), 1328 (C-N), 1226 (C-O).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.02 (s, 1H, OH), 7- 8.26 (m, 12H, Ar), 3.81 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3)

6) 2-(5-(4-chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)-5-methylphenol



IR (KBr) *v*: 3059(Ar C-H), 3345 (O-H), 2990 (aliphatic C-H), 1328 (C-N), 1226 (C-O).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.02 (s, 1H, OH), 7- 8.26 (m, 12H, Ar), 2.28 (s, 3H, CH_3)

7) 5-methyl-2-(1-phenyl-5-(p-tolyl)-1H-pyrazol-3-yl)phenol



IR (KBr) *v*: 3059(Ar C-H), 3345 (O-H), 2990 (aliphatic C-H), 1328 (C-N), 1226 (C-O).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.02 (s, 1H, OH), 6.89- 7.55 (m, 12H, Ar), 2.28 (s, 3H, CH_3)

Biological Activity

Compounds were screened for their antibacterial and antifungal activity using cup-plate agar diffusion method at a concentration of 40 mg, using Gram positive bacterial strains such as B. cocous and B.subtillus and Gram negative bacterium strain such as Proteus vulgaris and Escherichia coli. The antifungal testing was carried out against Aspergillus niger. Known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin, and antifungal activity was compared with Greseofulvin. The zone of inhibition measured in mm. By

visualizing the antimicrobial data, it could be observed that most of the compounds exhibited significant activity.

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3
Healthy hydroponic cattle feed (grass) development eco-friendly & economically

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Abstract

Dairy cattle require green fodder for high milk yield. However, it cannot available throughout the year and in some area, it is difficult to have access for green fodder. Thus, hydroponic fodder production has become an alternative way to fulfil this green fodder requirement of the dairy cow in low cost. According to WHO the production of milk in the India is 14 crore litres, but the consumption is 64 crore litres. It is being claimed that 68.7 percept of the milk and its products sold in the country are adulterated. In the US, the average dairy cow produces more than 7.5 gallons of milk per day and India's milk processing capacity is 126 million litres per day, the highest in the world, and lauded the dairy sector for increasing production from 22 MMT, or around 6 crore litres per day in 1977, to 58 crore litres per day in 2022. The adoption of this technique has enabled the production of fresh forage from grains without soil. Hydroponic fodder has high nutritive value due to the conversion of complex compounds into simpler and essential form, and activation of enzymes during germination. Thus, it contains high protein, vitamins and minerals which are essential for dairy cows. There were improvements in digestibility and intake of nutrients results in increased milk yields and quality like milk fat of dairy cow on the feeding of hydroponic fodder. Traditional fodder production has a number of limitations regarding soil & climatic conditions. In successful mulch animal rearing green fodder has its special significance.

Keywords: Hydroponics, Eco-friendly, Economics, nutritional value, Amino Acid.

Introduction

The word hydroponics has been derived from the Greek word "water working". Hydro means "water" and phonic means "working" and it is a technology of sprouting grains or growing plants without soil, but only with water or nutrient rich solution. However, hydroponics fodder can be well produced with the use of fresh water only It is one of the most important agricultural techniques currently in use for green forage production in many countries especially in arid and semi-arid regions environmentally control houses. The population of Dairy livestock has increased immensely in our country, but still it is unable to fulfil the required milk Demand that we need to import it. Dairy cattle require green fodder for being healthy and higher Milk yield. The facts that deficiency of feed and fodder alone Account nearly 50 percept losses in livestock. To overcome these hydroponic cattle feed cultivation is introduced. Hydroponics fodder production has two aspects i.e. Physiology and nutrition of plant-animal system and Engineering of hydroponic technology. Hydrophophic is the science of soilless growing of plants in Nutrient rich solutions at regulated temperature and humidity. The main problems of feed scarcity emanate from land scarcity; actually, rapid urbanization is the major cause behind the decrease in land meant for grazing and fodder cultivation. With Water, labour shortage and elevated cost of fertilizers the farmer leans to cultivate commercial food crops over green fodder. Nevertheless, producing green fodder to meet the current demand has become a greatest

challenge among livestock farmers. In fact, green fodder is very important for productive and reproductive performance of animals.
Feeding green fodder can improve livestock products. Livestock production in most regions is limited due to poor production and pricy imported green fodder. Today, land scarcity presents an important limit towards forage production for animal especially sheep, goats and cattle. Unlike monogastric mammals, ruminant cannot solely dependent on cereal grains. That's why, alternative technologies, such hydroponics, are regarded as vital to face these issues. The use of this technology can help improve the long-term economic development of the livestock industry. Hydroponic fodder can also improve the performance of the animals by providing their nutrient needs. Hydroponic growing green fodder has high feed quality, rich with proteins, fibres, vitamins, and minerals effects on animals. The growth of the fodder crop mainly depends on moisture, temperature, RH and irrigation. Hydroponic Green fodder is the natural diet for livestock. Hydroponic green fodder consists of grass with grains, roots, stems and leaves which are highly nutritious and provide sustainable fodder production and conserve water take 8 days to develop seed to green fodder. It's production to meet current demand has become a greatest challenge among livestock farmers, due to temperature, humidity and contamination on the seed and fodder are restrict the optimum growth of fodder. Amount of yield and quality of fodder is influenced by grain quality, grain variety and treatments and growing environmental. Green fodder production crisis serious problems which are contamination of seeds that effect germination, and plant growth. This contamination further takes to fungus and mould infection which are not healthy for livestock animals. Temperature, relative humidity is also parameter to increase and decrease the fungus and mould infection. Hydroponic farming means growing of plants without soil by using nutrients water at desired temperature and humidity. Through hydroponics it is easy and quick to produce nutritive green fodder. Green fodder is the natural diet for livestock. Its production to meet the current demand has become a greatest challenge among livestock farmers. Due to many reasons, green fodder production has been facing a serious crisis and so the livestock productivity. Due to increasing intensive system of rearing livestock, the need for green fodder is enormous .As the gap between the demand and supply of the green fodder for livestock becoming unconquerable, researchers and farmers are in search for an alternative fodder or fodder production method, that would restore fodder and livestock production.

Hydroponics is the state of the art technology that has revolutionised the green fodder production in the 21st century. Hydroponics is a method of growing green fodder without soil in an environmentally controlled houses or machines. Many of the livestock farmers are switching to hydroponic fodder production from conventional production methods, as the fodder produced by this method are highly nutritious, provide sustainable fodder production round the year and conserve water. Though this method has made a greatest impact in the fodder production system, most of the farmers are facing some practical difficulties in profitably running the hydroponic machine for sustainable fodder production. This manual has been compiled with the essential manage mental practices that have to be carried out for an economically sustainable fodder production. Green fodder plays major role in feed of all livestock. Also, into the milch animals, Green fodder providing required nutrients for milk production and health of the dairy animals. Green fodder feeding to livestock is important for optimization of productivity. Animals Feeding and fodder production are the two important aspects for the sustainability of products and productivity in animal rearing. Although, India is the top producer of milk in the world But there are many challenges insufficient livestock feed, fodder is one of the constraints Affecting growth, health, production and reproduction potential of livestock. Green fodder is the natural diet for livestock. Its production to meet the current demand has become a greatest Challenge among livestock farmers. Due to many reasons, green

fodder production has been Facing a serious crisis and so the livestock productivity. Due to increased population day by Day hence agriculture land is converted into urbanization. Now days small land holdings Amongst farmers, non-availability of irrigated lands for fodder production is reduced, Unavailability of fertile land for fodder production, increasing mining and coastal line has Limited area for fodder production, deforestation, lack of scientific knowledge of feed and Fodder production among unemployed youths for fodder farming, higher labour cost and Small land holdings has left livestock as well as dairy farmer with many challenges for Animal rearing and milk production in all over the world. Also, due to increasing intensive System of rearing livestock, the need for green fodder is huge. To overcome all these shortage Issue of green fodder the new hydroponics technology came into exist. Hydroponics is the state-of-the-art technology that has revolutionised the green fodder production in the 21st century. In India only 4.9% of cropped land area is utilized for cultivating fodder. Indian livestock industry faces a deficit of 35.6% green fodder, 26% of dry fodder and 41% of concentrate feed ingredients.

Problem statement

A suitable combination of green & dry fodder is Very important for maintaining animal health& milk production. But in Scarcity condition traditional green fodder production become impossible Because of lack of irrigation water. In such condition the technique of Green fodder production by Hydroponic method is very useful tool. This technique does not require soil. Hence limitations like Saline soil, inferior soil, water logged soil etc can be easily overcome. This Technique requires very less quantity of water. Hence it can be easily undertaken in scarcity affected areas. Green fodder is the natural diet of cattle. Green fodder is the most Viable method to not only enhance milk production, but to also bring about A qualitative change in the milk produced by enhancing the content of Unsaturated fat,, Omega 3 fatty acids , vitamins, minerals and carotenoids. Hydroponics fodder growing is the state-of-the-art technological Intervention to supplement the available normal green fodder resources required by the dairy cattle. The contamination was starts from the seeds. When seeds were soaking for 24 hours in water there was problem of fermentation and because of that the fermented odour take place to the seeds which are resulted the fungus infection. After soaking the seeds, the seeds were placed into gunny bags at dark rooms for sprouting this resulted increase in fermentation odour. Sprouted seeds when placed into the hydroponic or office tray water sprayed to the seeds were for 2 minutes which are 1liter/min and because of that the maize seeds had higher amount of water which are not suitable for fodder and the water are not well drained from the trays this causes increase in fungus infection. Uncontrolled environment was also helping to increasing the fungus infection if there is temperature is greater than 35 °c and humidity higher than 70 to 80 % the fungus and mould infection were increases.

Materials and Method/procedures

Hydroponics fodder unit is nothing but a chamber with arrangement of temperature, humidity and light intensity for maximum sprouting & growth of fodder crop seeds (mainly maize, oat, barley, wheat etc). With 30 to 35 ˚C temperature, 60 to 75 % R humidity and 50 % shed 1 Kg of maize should yield 6 to 8 Kg green fodder in 7 to 9 days. It found that for 6-8 times mass increase around 2 litre water is sufficient per kg of seeds during summer season. So by this one can grow very good, healthy & economical viable fodder for dairy / goat farming. (We suggest to calculate economic output of system at your end based on input seed cost) There are plenty of manufacturer suppliers of hydroponics systems in market but farmers can build their own system as it’s very easy to fabricate & all components available in market.

Following are required components with their specifications -

System components – Growing cabinet, Racks for trays, trays, seeds, watering system (fogger / mister / drip pipes) , timer, motor. (Photo look like are given below)

Growing cabinet – Square shape cabinet is most suitable & easy to fabricate , cabinet size can vary based on number of trays , cabinet can be fabricated with mild steel pipes (MS) , UPVC or bamboo. Just make square box and trays arrangement. Slotted angle racks can also be serve purpose. Cabinet need to be covered with 50 % green shed net and/or poly house covering film for reducing light intensity & conserves humidity.

Racks for trays – Can be of MS, UPVC or bamboo. Height of the tray racks need to be arranged as per day cycle of fodder i.e lower level 2 racks with 6 inch , above 2-3 racks on 8 to 12 inch and upper level racks 12 to 15 inch height. A gentle slope is beneficial for avoiding water lodging and fungal growth.

Trays – Various kind of trays are available in market based on quality of plastic & durability, specialized hydroponics trays are costly (2 feet * 2 feet tray cost approx. Rs.350) . We can use simple office tray (1.5 feet *1 feet) with perforations at bottom (simply drill holes on equal distance). Make sure there are sufficient holes made to avoid any kind of water lodging and avoid fungal infection. After every use, trayneed to be disinfected by diluted hydrogen peroxide and sun drying.

Seeds – Maize, wheat, oat, barely suits best for hydroponics. You can choose based on availability and rate per unit. Seed should be free from any fungal infection. To remove broken seed, give brine water treatment and remove floating seeds. Soak seed further hours in potassium permanent. Once seeds spouted 2 treatments of powder tricoderma Species will also help in lowering fungal Infection. Seed rate of 0.5 Kg / Ft2 is sufficient for hydroponics fodder cultivation.

Watering system – Motor pump of 0.25 or 0.5 Hp is sufficient for 100 tray system. For lesser Capacity, minimum 0.25 Horse power motor will be required for operating fogger / misters. We prefer Jain Irrigation misters than foggers as they required less pressure & easy for maintains. Drip line – regular 16 mm HDEP drip line is best suited.

Timer – Various timers available in market. Timer best suited are generally 1 to 2 min operation Every / hour. We prefer Frontier TM-619-H-2 with 17 time intervals. If motor pump is above 3 Amp Additional really is preferable.

Engineering Aspects of Hydroponic Technology – Research in the following areas of engineering and machinery development will help in making the system more acceptable to the farmers.

Reservoir Engineering and Nutrient Solutions- The reservoir is the part of the hydroponic System that holds the nutrient solution. Depending on the type of hydroponic system, the Nutrient solution can be pumped from the reservoir up to the growing chamber (root zone) in cycles using a timer, as well as continually without a timer. Reservoir can be made out Of materials including the plastic that can hold water. Nutrient solutions can be developed separately for hydroponic fodder crop and sprouted grain crop.

Delivery System-The delivery of the hydroponic system’s nutrient solution/water can be customized as per local needs.

Submersible Pump- Most hydroponic systems use a submersible pump to pump water/ Nutrient solution from the reservoir up to the growing chamber/root zone of the plants.

Air Pump- Other than in water culture systems, air pumps are optional in hydroponic Systems. However, using them has benefits. It helps to increase dissolved oxygen levels in the water up and keep the water oxygenated. This helps in keeping the nutrients evenly mixed all the time.

Grow Lights- Grow lights are optional part of hydroponic systems. One can choose to either Use natural sunlight or artificial light to grow the plants depending on the place of operation of the hydroponic system. These are generally used in commercial hydroponic systems for Growing fruits, vegetables and flowers.

Conclusion:

High initial investment on fully automated commercial hydroponic systems and high labour and energy costs in maintaining the desired environment in the system adds substantially to the net cost of hydroponic fodder production. Such systems are not successful in developing countries. Conversely, low cost hydroponic systems have been developed by utilizing locally available infrastructure where there is an acute shortage of fodder and water; local irrigation systems are not well established; transportation and fuel costs are high; and seasonal variations of fodder prices are extreme. Typical lean periods of fodder production are the norm, investment in controlling temperature and humidity are low, and so is the cost of labour. Under such situations the cost structure is often shifted in favour of hydroponic fodder production, and it may find a niche in increasing livestock production. Hydroponics fodder is nutritious, palatable and digestible and can be grown in low cost techniques with locally home grown grains. Against impeding climate change and less availability land hydroponics fodder production is an effective alternative technology for sustainable livestock production in different agro climatic regions of India. The use of hydroponic culture modified the chemical composition of milk with respect to fat content, which is a desirable parameter. Moreover, principal component analysis revealed that with respect to proximate analysis, the quality of milk from cows from the GZ farm was superior to that of cows from the MT farm. The difference between minerals in the two farms may not be easily interpreted as the environment plays an important role, particularly with contaminants in the air, water, and soil. Further studies are needed to establish the effects of long-term feeding with different types of hydroponic fodder and to investigate the effects of these hydroponic fodders on the productive and reproductive performance of dairy cows. Further studies may be directed towards the development of feeding strategies with respect to the inclusion of hydroponic fodder under different agro climatic conditions. The challenges of Hydroponic fodder-cum-sprouted grain technology are enormous in producing quality green feed and fodder, and using it for value addition of products, such as milk rich in CLA, Omega-3, vitamins and micro minerals; cage-free poultry products, grass-fed meat and meat products. Better outcome will be possible with the strong policy support and technology back up. When used as supplement in the feeding of dairy animals, it will improve health and reproduction; boost productivity as well as nutritional quality of milk and other foods of animal origin, thus improving the income and profits of the farmers. However, before adoption of hydroponic feed/fodder on wider scale, several issues pertaining to HPFP technology, namely, economics, viability, sustainability and superiority of hydroponic Fodder require further research on priority.

Result and Discussion

For sustainable dairy farming, quality green fodder should be fed regularly to dairy animals. Hydroponic fodder is a good option in front of the farmer because it grows fast, it contains a high nutrient value, and the most important thing is animals like to eat. Green fodder is an important constituent in the feed of livestock. Due to many drastic Changes in agriculture

system, animal rearing and increased population there is shortage of Green fodder to the livestock. Green fodder production through hydroponics technology can be a real beneficial alternative source to overcome the fodder deficiency in livestock sector with many advantage. In developed countries where there is no dearth of quality feed and fodder, the hydroponic production of fodder is less competitive than traditional fodder production when compared on per kg dry matter basis.

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4

Design and Synthesis of Heterocyclic Active Moieties of Pyrazoles and Its Importance's

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Abstract

Pyrazoles have totally concerned and great attention in organic and pharmaceutical fields, due to their promising value as synthetic intermediates for the generation of various bioactive compounds, Subsequently, the synthesis of pyrazoles is a significant focus on research for synthetic organic chemists. Similarly, fused pyrazoles such as pyrazolo based pyridines and pyrazolo pyrimidines have been broadly studied due to their various physiochemical and biological utilities based on the important structural electronic properties of these N-heterocyclic compounds. So, the synthesis of these fused heterocycles and of their derivatives is of distinguished interest to both reveal novel derivatives and exposed the new application. Several procedures have been explained in the literature for the preparation of pyrazoles and of their fused systems in recent years, which mostly involve condensation reactions. And the synthesized pyrazole-based derivatives were confirmed by ^{1}H NMR and GCMS analysis.

Keywords: *Pyrazole, N-Heterocyclic, bioactive, fused heterocycles*

Introduction

Heteroaromatic compound pyrazole compound of 5-membered ring having two adjacent nitrogen atoms [1]. NH-Pyrazoles are weak bases and also weak acids because they have tendency to accept the protons (C=N) and also nitrogen atom (N-H) in pyrrole have tendency to donate protons. [2] Similarly, the interaction between the heteroatoms and hydrogen i.e., hydrogen bonding is depending on structural units of pyrazoles [3].

A German chemist Ludwig Knorr in 1883, who tried to prepare the quinoline compound with antipyretic activity [4]. But unfortunately synthesized the pyrazole instead to quinoline [5]. Knorr has first familiarized the of pyrazole to this heterocycles core to represent that it was derived from pyrrole by the replacement of carbon atom by nitrogen [6]. the first to notice antipyretic action of pyrazole-based compounds in man, which has encouraged the interest in pyrazoles moiety [7]. Then in 1846, the Kosuge and Okeda extracted (a plant which is having antimicrobial activity), 3-n-nonylpyrazole from Houttuynia cordata and also levo-β-(1-pyrazolyl) alanine from watermelon seeds (Citrullus vulgaris) [8]. Until these findings it was thought that pyrazoles could not be found naturally [9]. The adaptability of pyrazole moiety-based compounds in biological utilities as well as synthetic also. It has been well recognized, being even one of the furthermost studied compounds among the azole family, even though there are so many natural products containing the pyrazoles moiety [10].

A N-heterocyclic compounds as like composed pyrazoles, substitutes pyrazoles are important due to their wide applications [11]. Most of natural products shows the presence of fused pyrazole structure. A compound pyrazolo[4,3-d] pyrimidine is naturally present in Formicin A. Which is having different biological activity. Such as antiviral and antitumor.

In over-all, biological and pharmacological activities of these compounds containing pyrazole core moiety fused with five- and six-membered heterocyclic compounds. In particular, pyrazole-based pyridine and pyrimidines have taken part in drug discovery [12].

EXPERIMENTAL SECTION

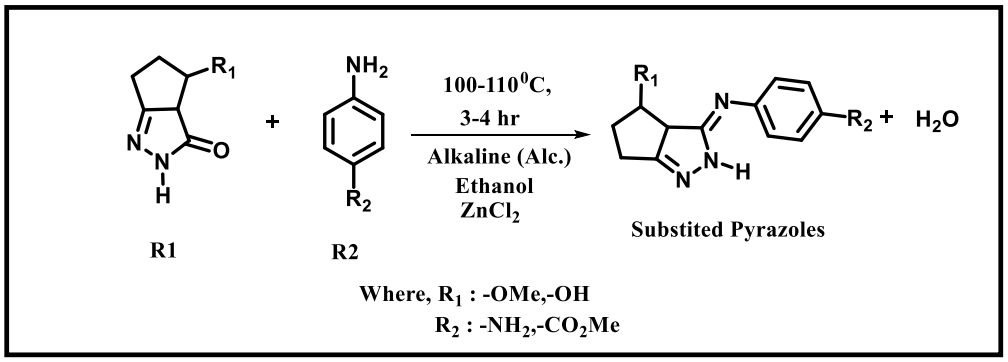
MATERIALS

Methanol (98%), Ethanol (98%) Acetonitrile (99%) and ethyl acetate (98%) were procured from Avra chemical Pvt. Ltd. Sodium hydroxide (98%) zinc chloride Were acquired from Sisco Research Laboratories Pvt. Ltd.

CHARACTERIZATION TECHNIQUE

The Chemical structure of synthesized compounds was confirmed by spectral data. ^{1}H-NMR spectra were recorded on BRUKER AVANCE NEO 500 MHz spectrometer using DMSO and $CDCl_3$ solvent and TMS as internal standards at SAIF, Punjab University, Chandigarh (India). Chemical shifts are expressed in ppm. Mass spectrums were recorded on Thermo Scientific TSQ 8000 Gas Chromatograph

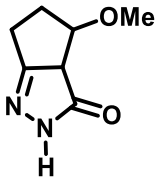
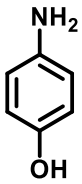
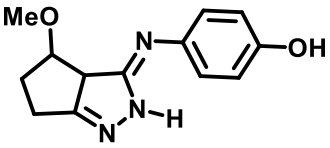
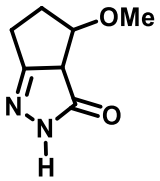
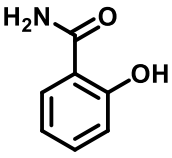
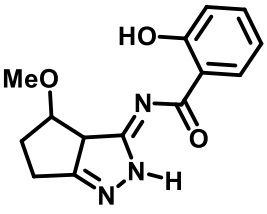
General Reaction



Scheme 1. General Reaction for Synthesis of N-Heterocyclic Substituted Pyrazoles

Reactant (R1) (0.1 mmol) was heated with reactant (R2) (0.15 mmol) in oil bath at 100 ºC to 110 ºC, till complete removal of dehydrated water is ensured. The solid cream color precipitate was obtained and it filtered, washed with methanol and recrystallized by ethanol with preferable yield, m.p.-178ºC as cream- white colored crystalline solid. (Scheme 1.)

Table 1. Synthesis of N-heterocyclic Pyrazoles Derivatives

Sr. No	R1	R2	Product	Time in Hrs.	Yield
1				4	86
2				4	81

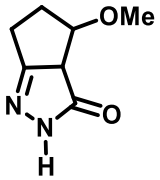
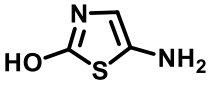
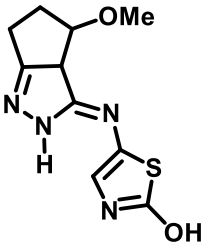
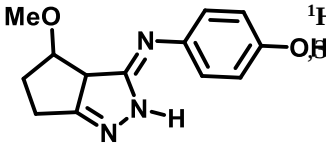
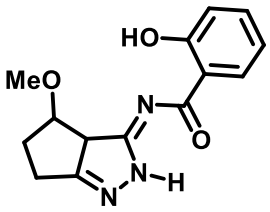
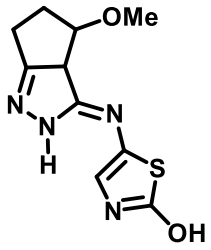
3				4	87

Table 2. Structural analysis of derivatives

Sr. No	Structure of Products	Structural analysis by ^{1}HNMR and GCMS
1		**^{1}HNMR(500MHz,CDCl$_3$)**:δ9.40(s,1H),6.747.20(m,4H),3.41(s,3H),3.2(q,1H),2.0-2.16(t,2H),1.56-1.81(t,2H),1.6(t,1H) **GCMS:** Cal m/z: 245.28, Found m/z: 244.16
2		**^{1}HNMR(500MHz,CDCl$_3$)**:δ16.4(s,1H),6.747.68(m,5H),3.41(s,3H),3.2(d,1H),2.0-2.16(t,2H),1.56-1.81(t,2H),1.6(t,1H) **GCMS:** Cal m/z: 273.11, Found m/z: 273.06
3		**^{1}HNMR(500MHz,CDCl$_3$)**:δ9.69(s,1H),7.68(s,1H),6.68(s,1H),3.41(s,3H),3.2(q,1H),2.06-2.16(q,2H),1.56-1.81(m,2H),1.6(t,1H) **GCMS:** Cal m/z: 252.29, Found m/z: 251.40

Conclusion

Synthesis of pyrazole derivatives and even their various functional group substituents are well established. Mostly, the bioactivity of the pyrazole derivatives was studied in detail. There are recent attempts in understanding different properties of the pyrazole derivatives. In addition, there are some challenges to overcome. These challenges include efficiency for high yields in synthesis, generating novel pyrazole derivatives with bioactivity in the sub micromolar range, and characterizing the properties of the derivatives accurately. For this reason, we believe there is a need for investigating new synthetic routes, studying different properties and seeking new applications of novel derivatives especially in blends with polymers. Therefore, the new trend in pyrazole derivatives will be towards new applications in various areas.

Acknowledgement

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Conflict of Interest: None

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5

QSAR analysis of sodium glucose co–transporter 1 (SGLT1) inhibitors for anti-hyperglycaemic lead development

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Abstract: GA-MLR **based** QSAR evaluation has been effectuated on a small dataset of **SGLT1 inhibitors** abide by OECD principles. Recent study revealed that the presence of *o*-xylene moiety, hydrogen atoms exactly five bonds from hydrogen bond donor atoms and ring carbon atoms within 2Å from hydrogen bond donor/acceptor atoms facilitate the SGLT1 inhibitory action of the compound. Developed QSAR models shown excellent performance on all the statistical parameters with values well above the approved thresholds, such as, R^2 = 0.79- 0.80, Q^2_{LOO} = 0.77, Q^2_{LMO} = 0.76, Q^2F^n = 0.87–0.90, CCC_{ext} = 0.93-95. Applicability domain
analysis and Y-randomization test also enhanced the credibility of this study.

Keywords: QSAR, SGLT1, anti-hyperglycaemics.

ABBREVIATIONS:

CADD- Computer **A**ided **D**rug **D**esigning, **SGLT1/2 -** sodium glucose co–transporter **1/2**, **SMILES- S**implified **M**olecular-**I**nput **L**ine-**E**ntry **S**ystem, **GA- G**enetic **A**lgorithm, **MLR- M**ultiple **L**inear **R**egression, **QSAR- Q**uantitative **S**tructure-**A**ctivity **R**elationship, **QSARINS**- QSAR Insubria, **OECD- O**rganization for **E**conomic **C**o-operation and **D**evelopment, **OFS- O**bjective **F**eature **S**election, **SFS- S**ubjective **F**eature **S**election

1. INTRODUCTION

SGLT1 and SGLT2 play crucial role in renal glucose re-absorption. SGLT1 is present in both the renal tubules and small intestine and are responsible for active glucose absorption. SGLT1 is a low-capacity glucose transporter (relative to SGLT2), its higher glucose affinity than SGLT2 and additional galactose transportation capability has own an identity of anti-

hyperglycaemic target to SGLT1. Dual SGLT inhibitors i.e. inhibitors of both SGLT1 and SGLT2 are under clinical trial and unfortunately no SGLT1 inhibitor based drugs in the market are present.

C-phenyl 1-thio-D-glucitol scaffold based derivatives [10,11], Deuterated C-Aryl Glycoside[12], Indole-N-glucoside (TA-1887)[13], 1-methoxy-6,8- dioxabicyclo[3.2.1]octane[14], benzocyclobutane-C-glycosides[15], 6-hydroxyl C-aryl glucoside derivatives[16], benzocyclobutane-C-glycosides[17], 6-deoxy O-spiroketal C-arylglucosides [18] are some classes of compounds tested for SGLT1 inhibitory potency. But the search of sufficiently potent SGLT1 inhibitor with no or minimum side effect is still on. To contribute to the development of better SGLT1 inhibitor L. Burggraaff did attempt to identify SGLT1 inhibitors in silico (Burggraaff et al., 2019) with the application of proteochemometrics through machine learning. There is still huge scope for the development

of SGLT1 inhibitors as possibly effective anti-hyperglycaemic agent.

2. MATERIALS AND METHODS

A. *Selection of data-set*:

For the present work, 107 C-aryl glucoside derivatives with in vitro SGLT1 inhibitory activity in terms of half-maximal inhibitory concentration i.e. IC_{50} = 0.4 to 100000 nM were used [19- 22]. The dataset consists of benzocyclobutane-C- (Placeholder1), deuterated C-Aryl Glycoside, series of C-phenyl D-glucitol derivatives, 6-deoxy *O*-spiroketal-*C*-arylglucosides, C-phenyl 1-thio-D-glucitol, and C_5-fluoro-hexose derivatives. A dataset truly comprised of diverse set of molecules with plenty of pharmacophoric features embedded along with the different scaffolds and hence has covered large chemical space. A QSAR model developed using such a dataset will certainly have large applicability domain that cover the class of the compounds presently under the process of optimization towards more potent SGLT1 inhibitors to treat hyperglycaemia.

The IC_{50} values in nanomolar (nM) unit were converted into molar (M) unit by multiplying factor 10^{-9}. The five least and the five most active C-aryl glucoside derivatives from the present dataset are depicted in **Figure 1** to demonstrate the variation in bio-activity with chemical features. The SMILES strings with the reported IC_{50} (in nM and M unit) and pIC_{50} values for all the molecules are given in Supplimentary information. Before QSAR analysis the I

IC_{50} :

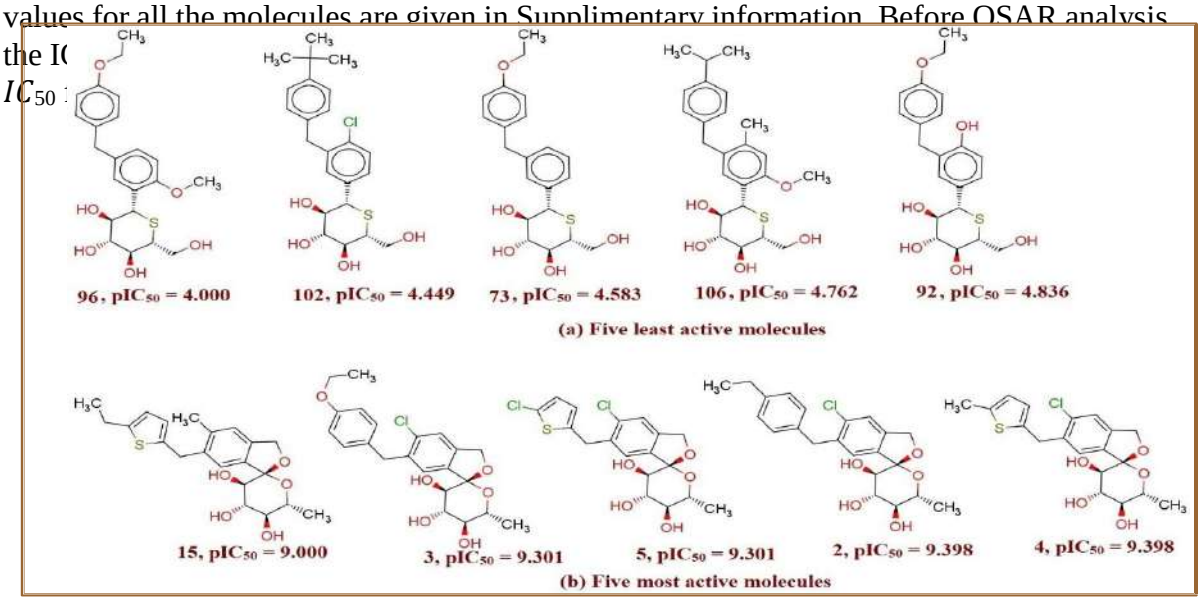


Figure 1: Variations in activity and chemical structure in the dataset used for development of QSAR Models

B. *Molecular Structure Drawing and Optimization:*

Free and open source software, ChemSketch 12 Freeware (www.acdlabs.com) is used to draw 2D structures and further conversion to 3D structures is achieved using OpenBabel

2.4.0. A geometry optimized molecule is characterized by its lowest energy i.e. most stable conformation. Geometry optimization ensures the normalization of all such a physico-chemical properties for all the molecules from dataset and makes it a necessarily important step prior to molecular descriptor calculation. As a step forward, force field MMFF94 available in TINKER is used for optimization of the molecules.

C. *Molecular Descriptor Calculation and Objective Feature Selection (OFS):*

A molecular descriptor is a structural and physico-chemical property of a molecule

or specific part of the molecule. More than 18,000 molecular descriptors were calculated for each molecule using PyDescriptor and PaDEL. In the data pruining step, Objective Feature Selection (OFS) in QSARINS v2.2.4 screened out multi-collinear and spurious molecular descriptors (i.e. with nearly constant values >95%, co-linearity |R| >0.95) and contracted molecular descriptor pool with 1145 variables is generated. Contracted though, molecular descriptor pool has covered adequately comprehensive chemical space being comprised of 0D– to 3D– descriptors, structural, constutional properties and charge descriptors etc.

D. *Subjective Feature Selection, QSAR Model – Development and Validation:*

In accordance with the OECD principles, firstly, apt variable selection method GA– MLR in Subjective Feature Selection (SFS) operation in QSARINS v2.2.4 is used to perform simple and easy to interpret QSAR models. Then, all the derived models were subjected to the thorough statistical validation, Y-scrambling and Applicability Domain analysis. The steps in QSAR building process:

I. Random split operation in QSARINS v2.2.4 split given dataset into a training set with 35 molecules (80%) and a prediction set with 9 molecules (20%) prediction. Molecules in training set were utilized for QSAR model development and external validation was performed on 9 molecules in prediction set.

II. QSAR models were built using Subjective Feature Selection (SFS) operation in QSARINS v2.2.4 (at default settings) by setting Q^2_{LOO} as fitness function. Insignificant increase in Q^2_{LOO} value was observed after 5 variables and hence to avoid overfitting SFS opertion is confined to 5 variables which additionally helped in deriving easy and informative QSAR models. (See supplementary information Table S2)

III. (a) Leave-One-Out (LOO) and Leave-Many-Out (LMO) parameter based internal validation; (b) External validation; (c) Y-scrambling and model Applicability Domain (AD) analysis, performed for legitimate validation.

IV. Performance of each model, measured by close inspection of the various statistical parameters meter the robustness of the GA-MLR based QSAR model. The QSAR model with best values of these parameters and with best predicative ability is selected.

3. RESULTS

Statistical QSAR

After removing all the insignificants terms, the following GAMLR QSAR model-1 and model- 2 were obtained from GA-MLR analysis.

GAMLR QSAR Model-1 (Training Set: 80% and Prediction Set: 20%)

$$pIC_{50} = 22.737(\pm 0.2.253) + 0.608(\pm 0.275)_\boldsymbol{ringC_2A} + 0.289(\pm 0.121)\boldsymbol{onH5B} - 0.466(\pm 0.173)\boldsymbol{ringS_C_8Ac} - 634.57(\pm 82.98)\boldsymbol{P.7}$$

GAMLR QSAR Model-2 (Training Set: 80% and Prediction Set: 20%)

$$pIC_{50} = 18.274(\pm 0.2.440) + 0.657(\pm 0.308)\boldsymbol{KRFP3596} + 0.258(\pm 0.116)\boldsymbol{fdonH5B} - 0.206(\pm 0.073)\boldsymbol{fringSH6B} - 424.535(\pm 82.051)\boldsymbol{P.7} \quad (1)$$

Statistical Parameters	Values	
	Model 5.1	Model 5.2
FITTING		
R^2	0.79	0.80
$R^2_{adj.}$	0.78	0.79
$R^2 - R^2_{adj.}$	0.01	0.01
LOF	0.32	0.32
K_{xx}	0.22	0.23
ΔK	0.14	0.15
$RMSE_{TR}$	0.52	0.51
MAE_{TR}	0.40	0.39
RSS_{TR}	22.85	22.48
CCC_{TR}	0.88	0.89
s	0.53	0.53
F	77.42	79.01
INTERNAL VALIDATION		
Q^2_{LOO}	0.77	0.77
$R^2 - Q^2_{LOO}$	0.02	0.03
$RMSE_{CV}$	0.55	0.54
MAE_{CV}	0.42	0.41
$PRESS_{CV}$	25.60	25.53
CCC_{CV}	0.87	0.87
Q^2_{LMO}	0.76	0.76
$R^2_{Y_{SCR}}$	0.05	0.05
$RMSE\ AV_{Y_{SCR}}$	1.10	1.10
$Q^2_{Y_{SCR}}$	-0.07	-0.07
EXTERNAL VALIDATION		
$RMSE_{EXT}$	0.36	0.40
MAE_{EXT}	0.32	0.35
$PRESS_{EXT}$	2.78	3.43
R^2_{EXT}	0.90	0.88
Q^2_{F1}	0.90	0.87
Q^2_{F2}	0.90	0.87
Q^2_{F3}	0.90	0.87
CCC_{EXT}	0.95	0.93
$r^2_m avg.$	0.85	0.76
$r^2_m delta$	0.03	0.13
k'	1.00	0.99
k	1.00	1.00

The statistical parameters for developed GAMLR QSAR models 1 and 2 have been presented in **Table 1**. A good number of statistical parameters for model 1 and 2, which are related to fitting, internal and external validation and Y-scrambling, have been calculated. From **Table 1**, it is clear that R^2_{TR}, CCC_{TR}, CCC_{cv}, R^2_{adj}, and F satisfy the recommended threshold value, which shows that the QSAR models are statistically robust with adequate number of molecular descriptors in the models. Although the data are obtained from different publications, they pass the statistical compatibility as the values of statistical parameters for fitting criteria such as R^2_{adj} = 0.78, R^2-R^2adj = 0.01, LOF = 0.32, CCC_{TR} = 0.88, etc. are well above the approved threshold values for both models. From Fitting parameters such as, R^2_{TR}, CCC_{TR}, CCC_{cv}, R^2_{adj}, and F satisfy the recommended threshold value which shows that the QSAR models are statistically robust with adequate number of molecular descriptors in them. The values for different cross-validation parameters such as Q^2_{LOO}, RMSEcv, MAE_{cv}, CCC_{cv}, and Q^2_{LMO} support the statistical robustness of the QSAR models. The graphs; Experimental endpoint against Predicted endpoint for both the models [Figure 4a & 5a] and experimental endpoint against residuals [Figure 4b & 5b] represent the performance of the QSAR model 1 and 2, respectively, on both Training and Prediction set molecules.

The external predictive ability of the models is established by the high values of R^2_{EXT}, Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, and CCC_{EXT}. In short, the developed QSAR models fulfill the recommended threshold values for many internal and external validation parameters. In addition, for a better validation of derived models, the model applicability domain (AD) was assured by plotting Williams plots for models 1 [Figure 4b & 5b]. Therefore, these models are statistically robust and possess good external predictive ability. Moreover, fulfilment of recommended threshold values for many parameters as well as low R^2 value after Y-randomization indicate that the model is not developed by chance.

The performance of the QSAR Model 1 and 2 for

each molecule from used dataset is given in Supplimentary Information respectively. Compound 29 (Exp. pIC_{50} =7.036 Pred. pIC_{50} = 7.042, PMER value = 0.006, HAT i/i= 0.037) and 85 (Exp. pIC50 =7.456, Pred. pIC50 = 7.457,
PMER value = 0.001, HAT i/i= 0.1 10) are the best predicted for their pIC50 values by model 1 and 2, respectively. Both compound 29 and 85 fall well within the AD of respective models as reflected from HAT i/I values. Possible reason for the best bioactivity P for the compound 29 [**Figure 2]** might be the presence of simple structural features, molecular planarity in a side chain of the glucoside scaffold maintained by simple methyl substituent and a fused ring substitution (benzocyclobutane) that minimized the errors in the bioactivity Prediction due to conformational changes in the molecules. Compound 85 (**Figure 3**) is with more number of pharmacophoric feature with large number of hydrogen bond donor and acceptor atoms (O, N, etc.). This might have helped molecule to attain optimum value for the molecular descriptors wherefrom QSAR equation is developed in subjective feature selection.

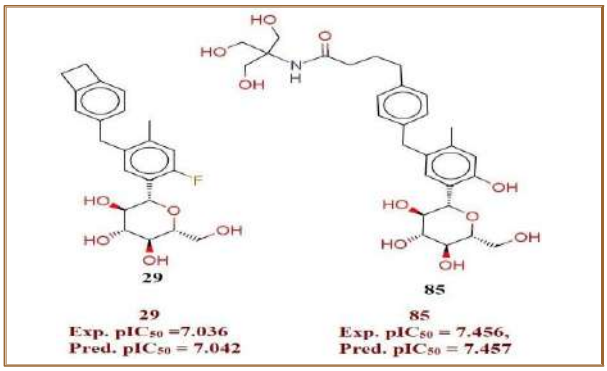


Figure 2: Representation of the best predicted compound by QSAR Model 1 and 2

Collective result of all these causes could be the reason for best SGLT1 inhibitory activity prediction for these compounds. Models developed in present study failed to predict precise bioactivity for some of the compound (see Figure 3). Compound 102 is the worst predicted compound (Exp. pIC_{50} =4.449 Pred. pIC_{50} = 5.784, PMER value = 1.335, HAT i/i= 0.038) for its SGLT1 inhibitory activity by model 1 whereas compound 45 is the worst predicted compound (Exp. pIC_{50} =5.933, Pred. pIC_{50} = 7.348, PMER value = 1.415, HAT i/i= 0.024) for SGLT1 inhibitory activity by model 5.2. In both the models, compound 14 is the third worst predicted compound (Exp. pIC_{50} =7.578, by model 5.1; Pred. pIC_{50} = 8.893, PMER value
=1.306, HAT i/i= 0.079 and by model 5.2; Pred. pIC_{50} = 8.858, PMER value =1.271, HAT i/i= 0.079).

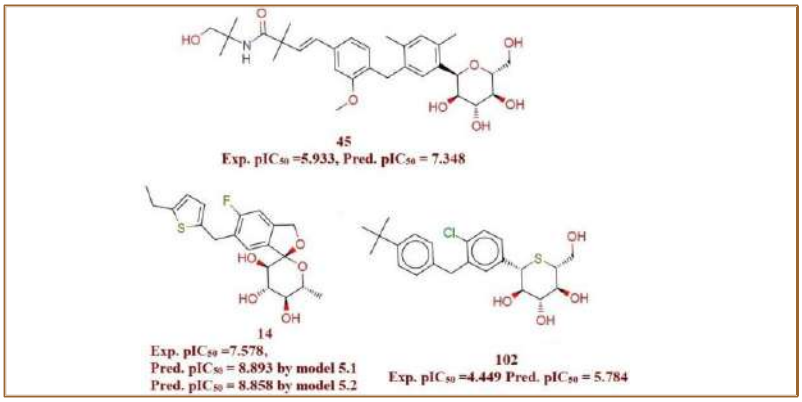


Figure 3: Representation of worst predicted and outlier compounds

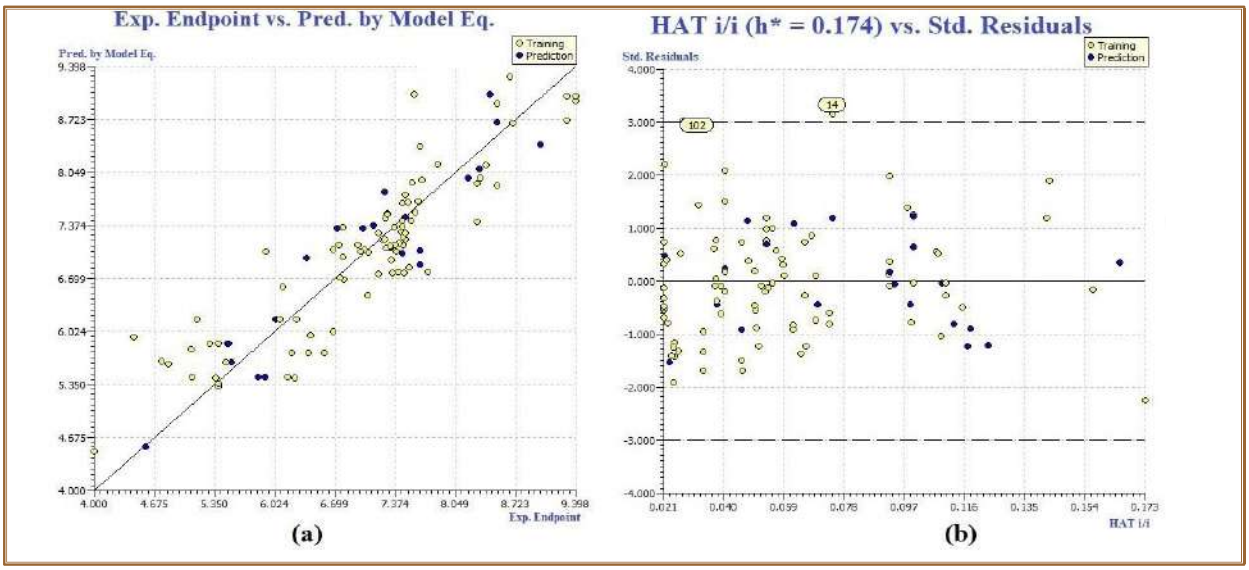


Figure 4: (a) Graph of Experimental vs. Predicted Endpoint values (b) Williams plot for QSAR Model-1

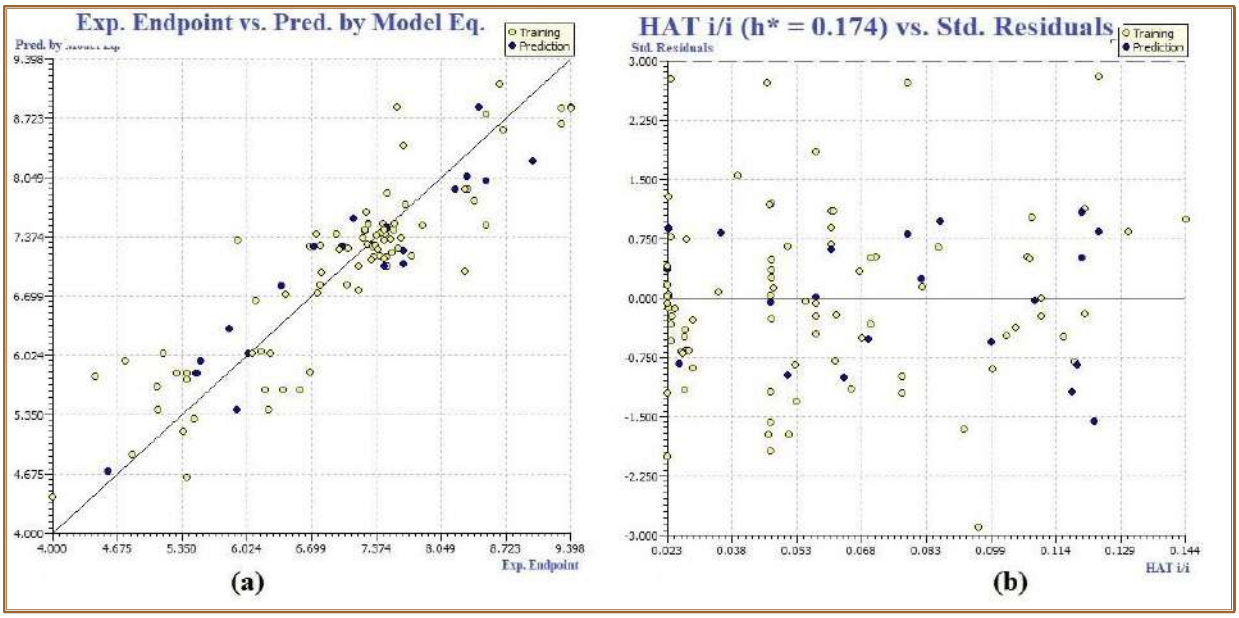


Figure 5: (a) Graph of Experimental vs. Predicted Endpoint values (b) Williams plot for QSAR Model-2

Descriptive QSAR fdonH5B

The molecular descriptor *fdonH5B* encode the information on frequency or number of Hydrogen atoms exactly five bonds from HBD atom. It has positive coefficient, thus increase in the value of *fdonH5B* increase the pIC_{50} value i.e. SGLT1 inhibitory potency of the compound. To support this observation, a pair of compound 44 (*fdonH5B* = 2; pIC_{50} = 6.754) and 30 (*fdonH5B* = 1; pIC_{50} = 6.686) is appropriate. Compound 17 (*fdonH5B* = 0; pIC_{50} = 8.301) and 16 (*fdonH5B* = 3; pIC_{50} = 8.398) is yet another pair of compound that appropriately support the same observation (Figure 6). The substituent –Cl in compound 17 on replacement by $–CH_3$ added three Hydrogens which got placed exactly five bond from HBD i.e. –OH group ortho glycoside residue.

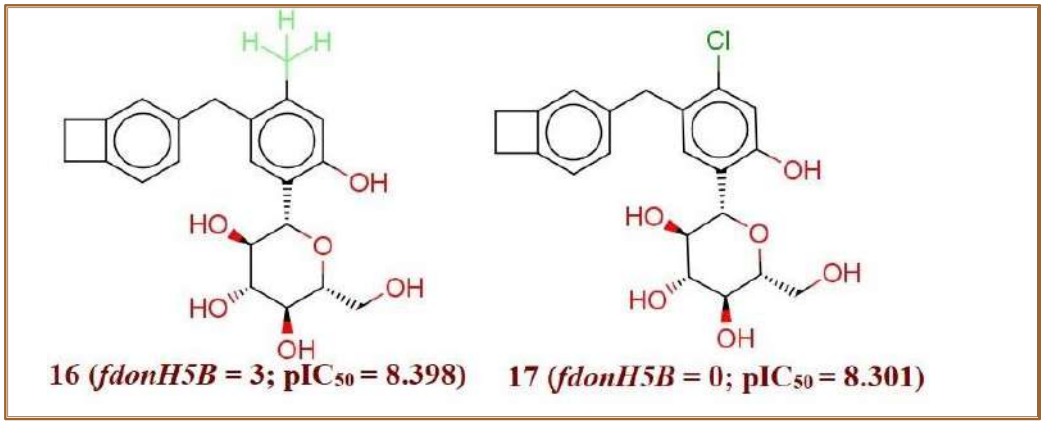
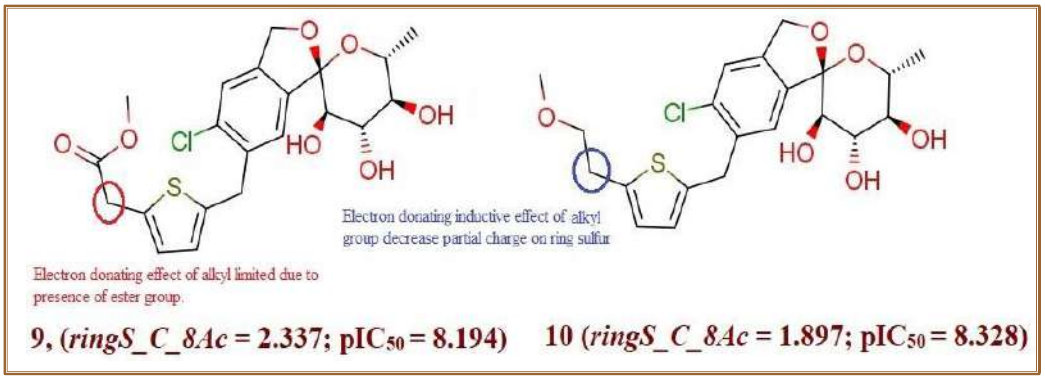


Figure 6: Illustration of the molecular descriptor fdonH5B

ringS_C_8Ac

The molecular descriptor *ringS_C_8Ac* encode the information on the sum of partial charges of ring Sulfur atoms within 8Å from C atom. As it has negative coefficient, decrease in the value of *ringS_C_8Ac* enhance the SGLT1 inhibitory potency of the compound. The significance of this molecular descriptor is highlighted by comparing compound 9 (*ringS_C_8Ac* = 2.337; pIC_{50} = 8.194) with 10 (*ringS_C_8Ac* = 1.897; pIC_{50} = 8.328) wherein decrease in the value of *ringS_C_8Ac* furnished more potent SGLT1 inhibitor (**see Figure 7**). The close observation of the structures of compound 9 and 10 reveal that this molecular descriptor indirectly provide information on substituency on ring containing Sulfur atom. In compound 9, the electron donating inductive effect of $–CH_2-$ group is limited by an electron withdrawing inductive effect of ester –C(O)O group whereas in compound there is ether functionality that too separated by one more CH_2 group and hence an electron donating effect of CH_2 group is retained. This feature in compound 10 diminish the partial positive charge on ring Sulfur.



da_ringC_2A

Figure 7: Illustration of the molecular descriptor ringS_C_8Ac

The molecular descriptor, *da_ringC_2A* encode the information on number of ring Carbon atoms within 2Å from HBD and HBA. It has positive coefficient and hence increase in the value of this descriptor cause increase in the SGLT1 inhibition activity of the compound. Comparison of compound 44 (*da_ringC_2A* =2; pIC_{50} = 6.754) with 30 (*da_ringC_2A* =1;
pIC_{50} = 6.686) rationalize the observation. Compound 48 (*da_ringC_2A* =3; pIC_{50} = 7.444) with 47 (*da_ringC_2A* =4; pIC_{50} = 7.638) is yet another pair of the compound to support this fact.

KRFP3596

It is a Klekota-Roth fingerprint abbreviated as KRFP. It encode the information on the presence of various chemical substructures. KRFP3596 molecular descriptor encode specifically the presence of substructure represented by *o*-xylene moiety (see **Figure 8**). This molecular descriptor has positive coefficient and hence the presence of *o*-xylene substructure own better SGLT1 inhibitory potency to the compound. This observation can be supported by the observation of whole dataset. All the most active compounds with $pIC_{50} \geq 7.036$. o-xylene substructure is present (KRFP3596 = 1) whereas in the least active compounds with $pIC_{50} \leq$
5.514 (with few exceptions) there is no *o*-xylene substructure present (i.e. KRFP3596 = 0). In **Figure 8** *o*-xylene moiety quantitatively encoded as KRFP3596 is depicted using compound 4 (a most active SGLT1 inhibitor of the series).

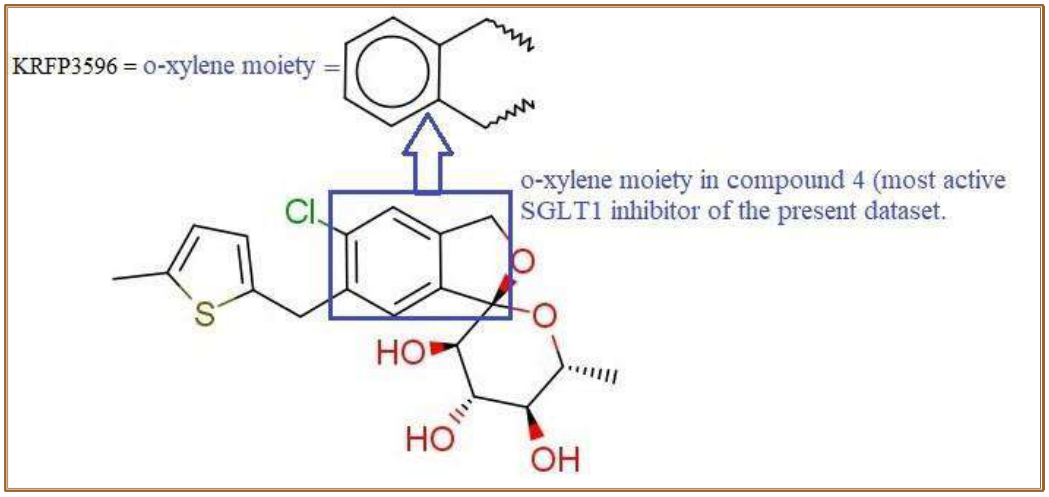


Figure 8: Illustration of the molecular descriptor KRFP3596

ASP.7

ASP.7 i.e. average simple path, order 7 abbreviated as *ASP.7* is one of the χ Chi Path descriptor. It has negative coefficient in both the models. Therefore, decrease in the value of *ASP.7* increase the value of pIC_{50} i.e. SGLT1 inhibitory potency of the compound. Significance of the smaller value of *ASP.7* molecular descriptor for better SGLT1 inhibitory potency is supported

by comparing compound 1 (*ASP.7* = 0.027, pIC_{50} = 7.652) with compound 2 (*ASP.7* = 0.026, pIC_{50} = 9.398). Decrease in the value of *ASP.7* by just 0.001 unit elevated the potency of compound 3 by about 1.7 unit.

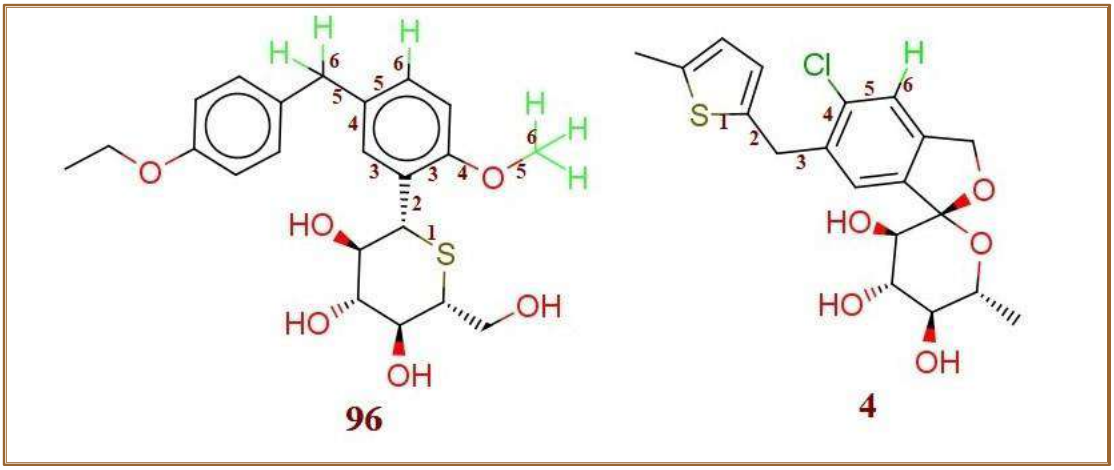
fringSH6B

The molecular descriptor, *fringSH6B* encode the information on the number of Hydrogen within 6 bonds from ring Sulfur. It has negative coefficient and hence decrease in the value of *fringSH6B* could increase the SGLT1 inhibitory potency of the compound. The least active SGLT1 inhibitor of the series i.e. compound 96 there are 6 such a hydrogens are present (**Figure 9**) and last 7 least active compounds have at least 2 such hydrogens (i.e. *fringSH6B* =2 in their structure. On the contrary, the 4 most active compounds of the series have only 1 or even no (0) such a hydrogens (**Figure 9)**. This molecular descriptor provide an easy ground for optimization of present SGLT1 inhibitors toward more potent leads. For example, in compound 4 (the most potent SGLT1 of the series) just repositioning of –Cl that replace hydrogen at 6 bond from sulfur could furnish more potent SGLT1 inhibitor. In case of presence of -OCH_3 group as a bearer of such hydrogens can be replaced by –OCF_3 or –OH group and more SGLT1 inhibitor can be expected.

Figure 9: Illustration of the molecular descriptor fringSH6B

4. CONCLUSIONS

Statistical accomplishment of both the models is quite satisfactory as reflected from values of the various statistical parameters that are well above the approve threshold values. High value of Q2LOO = 0.77, Q2LMO = 0.76, R2EXT = 0.88-0.90, and Q2Fn = 0.87-0.90 and



CCCEXT
= 0.93-0.95 mark the acceptable predictive ability of the Model 1 and 2. Applicability domain analysis based on leverage approach provided an information on the most appropriate classes of the compounds with distinguished scaffold and pharmacophoric features for reliable prediction of SGLT1 inhibition potential prior to their wet-lab synthesis and/or in-vitro/in-vivo

studies. Information on PMER values for all the compounds and best predicted compound(s) help to have precise guess on the predicted activity. The knowledge of worst predicted compound(s) and/or outlier(s) help the user to identify compound(s) unsuitable for the application of the models for reliable SGLT1 inhibitory potential.

Presence of o-xylene moiety, Hydrogen atoms exactly five bonds from HBD atom and ring Carbon atoms within 2Å from HBA and HBD atoms, facilitate the SGLT1 inhibitory action of the compound, as suggested by QSAR evaluations. In the course of optimization of the existing SGLT1 inhibitors within applicability domain of the models developed, it is advisable to ensure the more number of Hydrogens exactly five bond and ring Carbons within 2Å from HBA and/or HBD atoms. Introduction of ring substituent within 2Å from HBA and HBD atoms or substituting existing ring system with optimum number of functionalities with HBA and HBD atoms could suffice to have required structural modification and hence highly recommended during structural derivatization. QSAR evaluation also suggest that the ring

Sulfur atoms within 8Å from Carbon atom, Hydrogen atoms within 6 bonds from ring Sulfur are detrimental to the activity of the SGLT1 inhibitors. In the compounds from dataset, sulfur present in two different scaffold systems viz. S-glycoside ring and thiophene ring. It is observed that, occurrence of S-glycoside moiety set to zero towards the end of most potent SGLT1 inhibitors. However, thiophene has not proved that detrimental to SGLT1 inhibitory potency of the compound as it is present in some of the relatively more potent SGLT1 inhibitors. Removal of thiophene is not advisable but, it is suggestive to not to substitute thiophene ring with substituent that could intensify the positive charge on Sulfur of the thiophene through electron withdrawing inductive/resonance effect such as –Cl, -COR, -C(O)OR etc.

In conclusion, the present QSAR analysis was effective in identifying interdependent, interconnected astounding structural features which are otherwise hard to recognize by mere observation. Strategic optimization of the present SGLT1 inhibitors within applicability domain of the model with recommended Structural modifications could lead to the discovery of more active SGLT1 inhibitor(s) as an effective anti-hyperglycaemic agent with acceptable ADMET profile.

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6

Preparation and Acetone Gas Sensing Properties of Cd Substituted Magnesium Ferrites

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Abstract :

In this work, we report the preparation and gas sensing performance of pure and doped $MgFe_2O_4$ were prepared by sol gel method. The structural characteristics of the material were studied by using X-ray diffraction and Scanning Electron Microscopy. The XRD pattern shows a nanocrystalline solid solution of $MgFe_2O_4$ with an orthorhombic phase and the crystallite sizes is found to be in the range of 30-40 nm. The gas sensing performance of the unmodified and surface modified films was tested for various gases such as H_2S, NH_3, LPG and acetone. $Mg_{0.4}Cd_{0.6}Fe_2O_4$ powder showed large response to 200 ppm acetone gas at an operating temperature 180^0C. The sensitivity, selectivity of $Mg_{0.4}Cd_{0.6}Fe_2O_4$ thick films was measured.

Keywords: Acetone sensor, $Mg_{0.4}Cd_{0.6}Fe_2O_4$, Gas sensing properties, Response time.

1. Introduction:

Magnesium ferrites ($MgFe_2O_4$) have emerged as promising candidates for gas sensing applications owing to their inherent chemical stability, high surface area, and tunable electrical properties. The ability to detect volatile organic compounds (VOCs) such as acetone is of particular interest due to its relevance in various industrial, environmental, and healthcare sectors. However, enhancing the sensitivity, selectivity, and response time of gas sensors based on magnesium ferrites remains a key challenge.

Dopant-mediated modifications offer a promising strategy for tailoring the gas sensing properties of magnesium ferrites. Among the dopants explored for this purpose, cadmium (Cd) substitution has garnered significant attention due to its potential to influence the structural and electronic properties of the host material. By introducing Cd ions into the magnesium ferrite lattice, it is possible to induce changes in the surface morphology, defect structure, and gas interaction mechanisms, thereby enhancing the sensing performance towards acetone and other VOCs.

The detection of acetone gas holds immense importance in various applications, including industrial process monitoring, environmental pollution control, and medical diagnostics. Reliable and efficient gas sensors capable of detecting acetone at low concentrations are essential for ensuring workplace safety, environmental compliance, and early disease diagnosis.

Chemical methods [1-3], microwave sintering method [4,5], Citrate precursor method [6], wet chemical method [7] and Sol-gel method [8] etc. The sol-gel method has been identified as the most straightforward approach for preparing ferrites in bulk form. In this paper the results are presented of the ferrites prepared by using sol gel method.

The development of Cd-substituted magnesium ferrite-based gas sensors presents an exciting opportunity to address these challenges and advance the state-of-the-art in gas sensing technology. Structural properties of Mg^{2+} and Al^{3+} co-substituted lithium ferrites were studied by Modi et al [9]. X-ray and infrared studies of chromium substituted magnesium ferrite was reported by Kawade et al [10] and found that, the lattice parameters decrease with Cd^{3+} substitution and the X-ray density decreases as Cd^{3+} content increases. The distance between magnetic ions in both octahedral and tetrahedral sites decreases with increase in Cd^{3+}.

In this research paper, we present a systematic investigation of the preparation and acetone gas sensing properties of Cd-substituted magnesium ferrites. Through a combination of synthesis techniques, structural characterization, and gas sensing measurements, we aim to elucidate the influence of Cd doping on the microstructure, surface chemistry, and sensing performance of the synthesized materials.

2. Experimental Details

2.1. Material Synthesis

Analytical grade reagents were utilized throughout the experiment. Nanostructured $MgFe_2O_4$ and $Mg_{0.4}Cd_{0.6}Fe_2O_4$ were synthesized by the sol-gel method. Initially, a precursor was prepared using the sol-gel citrate method, employing the stoichiometric ratio of ferrous nitrate, magnesium nitrate, cadmium nitrate, and citric acid. This precursor was then dissolved in ion-free water at 80°C for 2 hours. Subsequently, ethylene glycol was introduced with continuous stirring to achieve a homogeneous and stable sol. The solution underwent further heating in a pressure vessel at approximately 130°C for 12 hours. Throughout this process, the transparent solution underwent a transformation into a gel state with notably high viscosity. The material was subsequently subjected to heating in a furnace at 350°C for 3 hours, resulting in a vigorous combustion that spontaneously propagated until all the gel was consumed, leaving behind a loose powder. This powder is calcination at 650°C for 6 hours to enhance the crystallinity of the materials.

2.2. Characterization techniques

The synthesized samples were characterized for their structure and morphology by X -ray powder diffraction (XRD; Siemens D5000) and Scanning electron microscopy (SEM; Hitachi-800). The X-ray diffraction data were recorded by using CuK_α radiation (1.5406 A^0).

2.3. Measurement of sensing properties

The gas-sensing properties of prepared $Mg_{0.4}Cd_{0.6}Fe_2O_4$ powders were studied for reducing gases such as H_2S, NH_3, LPG and acetone whose concentration were fixed at 1000 ppm in air. The gas sensitivity (S) was defined as: $S = (Ra - Rg)/Ra = \Delta R/Ra$; where, Ra and Rg are the resistance of sensor in air and the test gas, respectively. The gas-sensing properties were measured in a temperature range of 50 – 350^{0}C.

3. Results and Discussion

3.1. X-ray Diffraction Study

The XRD pattern of the $Mg_{0.4}Cd_{0.6}Fe_2O_4$ prepared by sol-gel method calcined at 650^{0}C is presented in Figure 1. Study of X-ray diffraction reveals that all the compositions under investigations were found to be face centered cubic spinel structure. The XRD pattern indicates that the product has high degree of crystallinity judged from the high and sharp diffraction peaks. The average particle size of the nanocrystalline $Mg_{0.4}Cd_{0.6}Fe_2O_4$ according to the scherrer formula were in the range of 30–40 nm.

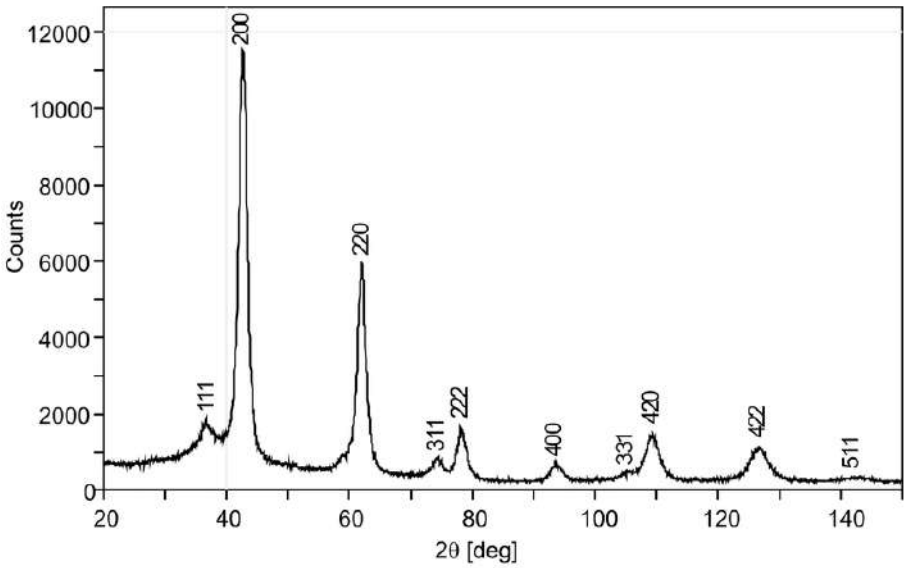


Fig 1 XRD pattern of $Mg_{0.4}Cd_{0.6}Fe_2O_4$ calcined at 650^{0}C

3.2 Scanning Electron Microscopy

The powder sample's morphology was examined using scanning electron microscopy (SEM). Figure 2 displays the SEM image of the $Mg_{0.4}Cd_{0.6}Fe_2O_4$ powder, revealing a uniform distribution of grain sizes with a slight tendency for agglomerate formation. The formation of polycrystalline material led to particle sizes ranging between 30 to 40 nm.

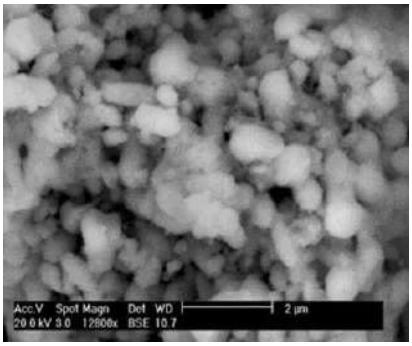


Fig 2 SEM image of $Mg_{0.4}Cd_{0.6}Fe_2O_4$ calcined at 650^0C

3.3. Gas Sensing Properties

Figure 3 illustrates the sensor response (S) plotted against the operating temperature for undoped $MgFe_2O_4$ nanopowder, which was calcined at 650°C for 6 hours, when exposed to different reducing gases such as H_2S, NH_3, LPG, and acetone. The sensor exhibits a notably higher response to acetone gas compared to LPG, NH_3, and H_2S at an operating temperature of 250°C.

To enhance the gas response properties, various atoms or additives are introduced into the base sensing semiconductor. Figure 4 illustrates the gas response concerning different amounts of Cd-doped $MgFe_2O_4$ (x = 0.2, 0.4, 0.6, and 0.8). The response to acetone gas exhibits a consistent increase with the rise in Cd concentration. The highest response is observed for $Mg_{0.4}Cd_{0.6}Fe_2O_4$ (x = 0.6) due to the increased availability of sites for oxygen adsorption, facilitating the oxidation of the test gas. Conversely, a decrease in response may stem from an inadequate number of available sites on the surface. The partial replacement of Mg by Cd ions leads to a reduction in grain size, resulting in a higher density of grain boundaries and consequently, an increased effective exposure area of the film to ammonia gas. Additionally, the chemical composition of the semiconductor is a critical parameter influencing its sensing performance. Indeed, the composition alone can impact the microstructure and thereby dictate the sensing properties.

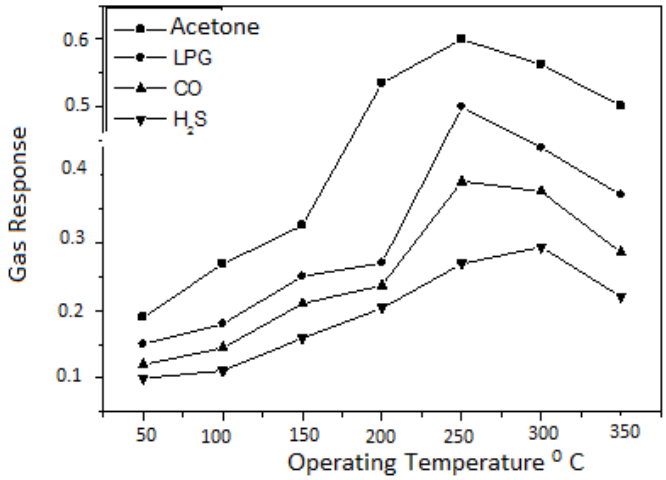


Fig 3 Gas sensing characteristics of undoped $MgFe_2O_4$ for various reducing gases as a function of operating temperature.

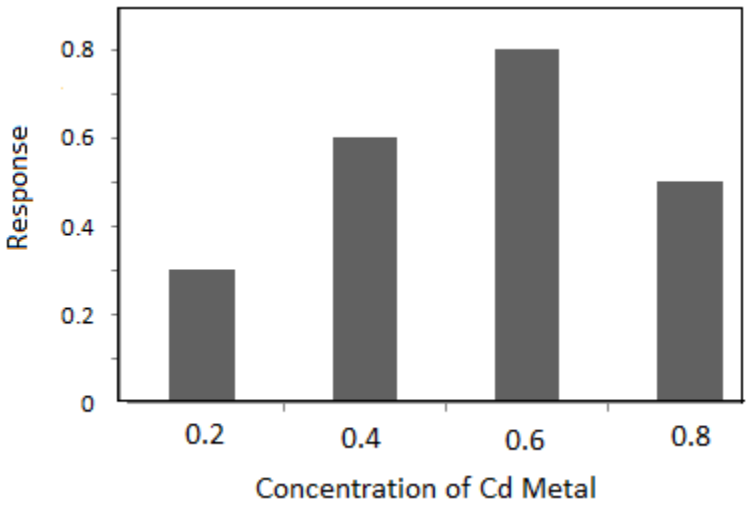


Fig 4 Sensor Response of $MgFe_2O_4$ doped with different amount of Cd calcined at 650^0C. (a) x=0.2, (b) x=0.4, (c) x=0.6and (d) 0.8

Figure 5 depicts the gas response of $Mg_{0.4}Cd_{0.6}Fe_2O_4$ across various operating temperatures. It is evident that the sensor exhibits a notably higher response to acetone gas compared to H_2S, NH_3, and LPG at 180°C. This heightened sensitivity to acetone gas can be attributed to the surface modification achieved by Cd over the $Mg_{0.4}Cd_{0.6}Fe_2O_4$ film. The enhanced selectivity can be elucidated as follows: Upon adsorption of O2- on the surface of $Mg_{0.4}Cd_{0.6}Fe_2O_4$, it captures electron(s) from the n-type semiconductive $Mg_{0.4}Cd_{0.6}Fe_2O_4$ body due to the strong electronegativity of the oxygen atom, resulting in the formation of negatively charged chemisorbed oxygen species such as O_2^-, O^-, and O^{2-}. Consequently, the electron concentration within the n-type $Mg_{0.4}Cd_{0.6}Fe_2O_4$ diminishes, thereby leading to an increase in the material's resistance.

Figure 6 shows the dependence of gas response of the $Mg_{0.4}Cd_{0.6}Fe_2O_4$ sensor on the concentration level of acetone gas at 180ºC. It is clear from the graph that with the increase in the concentration, the response increases linearly up to 200 ppm of acetone gas, after that it saturates. The graph also indicates that at low concentration response has a linear relationship with concentration because there may be sufficient number of available surface states to act on acetone gas. After 200 ppm level of acetone gas, the curve flattens because there would not be enough ionosorbed oxygen species to contribute to detecting mechanisms.

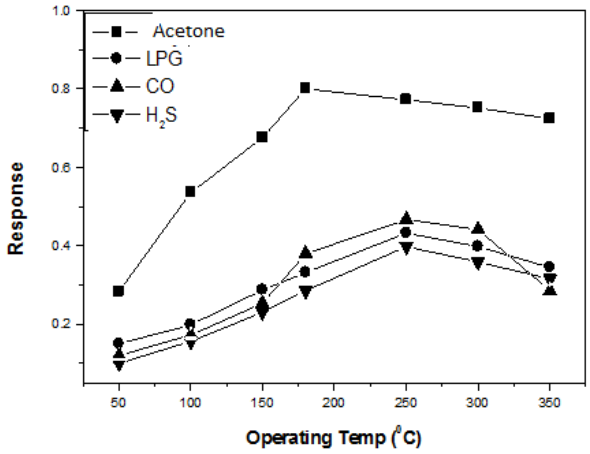


Fig 5 Response to different reducing gases of $Mg_{0.4}Cd_{0.6}Fe_2O_4$ as a function of operating temperature.

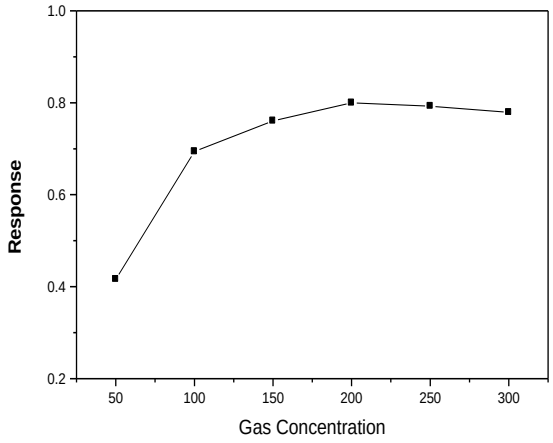


Fig 6 Response of $Mg_{0.4}Cd_{0.6}Fe_2O_4$ to acetone gas of different concentration at an operating temperature 180°C.

Figure 7 shows the response time of the sensor at 180°C. The response time in this case is ~ 40 sec. It was observed that the response time comes to saturated at 55 sec. It suggests that after this time there is no more O^- species left to react with the acetone gas vapour. It also indicates that by increasing the surface area i.e. increasing the grain size of the film, one can increase the response time.

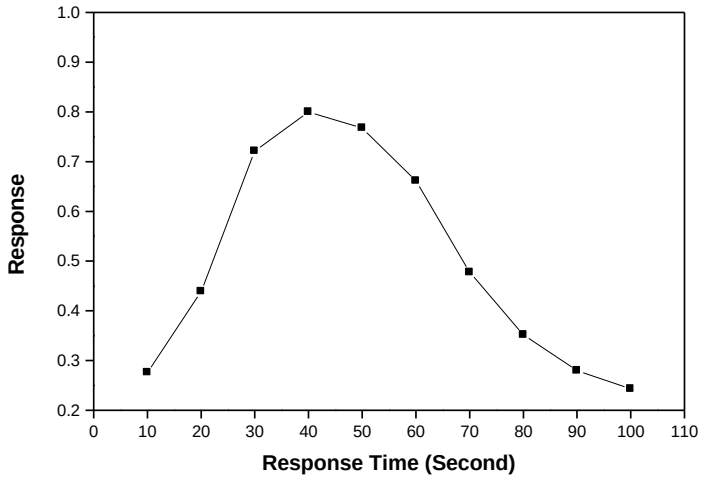


Fig 7 Response characteristics of $Mg_{0.4}Cd_{0.6}Fe_2O_4$ at 180°C.

4. Conclusion

In this study the preparation and gas sensing properties of both pure and doped $MgFe_2O_4$ materials synthesized through a chemical method. Structural analysis via X-ray diffraction and scanning electron microscopy revealed a nanocrystalline solid solution of $MgFe_2O_4$ exhibiting an orthorhombic phase, with crystallite sizes ranging between 30-40 nm. Gas sensing experiments were conducted on unmodified and surface-modified films, assessing their responses to various gases including H_2S, NH_3, LPG, and acetone. Specifically, $Mg_{0.4}Cd_{0.6}Fe_2O_4$ powder demonstrated a significant response to 200 ppm acetone gas at an operational temperature of 180°C. The sensitivity and selectivity of $Mg_{0.4}Cd_{0.6}Fe_2O_4$ thick films were also evaluated. These findings underscore the potential of $MgFe_2O_4$-

based materials for gas sensing applications, particularly in detecting acetone gas, with implications for diverse industrial and environmental monitoring scenarios.

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7

Studies of Acoustic Properties of Substituted Chalcone in Different Percentage of Dioxane-Water Mixture

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ABSTRACT--Ultrasonic velocity and density measurement of synthesized Dibromo chalcone ligand were carried out in different percentage of Dioxane-water mixture at 30 ± 0.1^0C. The obtained experimental data have been used to evaluate acoustical parameters such as intermolecular free length, specific acoustic impedance, relative association, adiabatic compressibility, apparent molal compressibility, and apparent molal volume. These parameters are used to interpret solute-solvent, solute-solute interaction in the system.
Keywords --- 1,4-Dioxane, ligand, Ultrasonic velocity, intermolecular free length,metal ions etc.

INTRODUCTION

The ultrasonic velocity technique is one of the most powerful techniques for studying the nature of intermolecular interaction in liquid. The ultrasonic velocity and other acoustic parameters can be measured with great accuracy and provides a powerful way to determine intermolecular interactions. The ultrasonic studies are useful in extensive research in different field of science [1-4]. This is because of its ability of characterizing physicochemical behaviour of liquid medium[5-6]. The measurements of ultrasonic velocity are helpful to interpreted solute- solvent, ion-solvent interaction in aqueous and non-aqueous medium[7-8].Numerous workers have done the acoustical study by the measurement of density and ultrasonic velocity of different aqueous and non-aqueous system at different temperature, different concentration of solute and in different percentage of organic solvent[9-11].The ultrasonic and viscometric studies of œ amino acids in different percentage of aqueous dioxane systems have been carried out by Raut et al[12]. The ultrasonic interferometric investigations of 3-(chloroaryl)-5-aryl-1-substituted pyrazolines in different percentage of dioxane medium at different temperature have studied by Deshmukh and Raghuwanshi[13]. They are reported that the ultrasonic velocity decreases with increase in percentage of organic solvent.Thorat S. A. and Thakur S. D.have studied the ultrasonic behaviour and molecular interaction of substituted 3,5-diaryl isoxazoline in different percentage DMF-water mixture at 305 K. They reported that there is weak solute-solvent interaction in all systems[14]. Deosarkar et al investigated the acoustical studies of some pyrazoles in different percentage of dioxane-water mixture at 303.15 k at 2 MHz frequency. They observed that the interactions are exist between pyrazoles and dioxane water mixture and solute-solvent interactions are more favorable than other interactions [15]. The ultrasonic behviour and study of molecular interactions of chalcone in dioxane at different concentrations and in different percentages of dioxane- water mixture at 305 K at 1 MHz frequency have been investigated by Pathare[16]. The present work deals with the effect of different percentage of Dioxane-water mixture on acoustical parameters of synthesized Schiff base ligand at 30 ± 0.1^0C.

EXPERIMENTAL

The Dibromo Chalcone ligand were synthesized in the laboratory by literature method [17]. All the chemicals used are of good analytical grade (AR). The solution of solute was

prepared by dissolving required amount of ligand in different percentage of purified Dioxane-water solvent. The acoustical parameters are determined at fixed concentration of solute 1 x 10^{-3} M. The density of solvent and solutions were measured by specific gravity bottle having 10 ml capacity. The ultrasonic velocities were measured by using ultrasonic interferometer having frequency 2MHz (Mittal Enterprises Model No. F-80).The constant temperature was maintained by circulating water through the double wall measuring cell, made up of glass.

THEORY AND CALCULATION

The sound velocity of ligand was measured in different percentage of dioxane-water mixture. The wavelength of ultrasonic wave is calculated using relation,

$$2D = \lambda \quad \text{---------- (1)}$$

Where, λ is wave length and D is distance in mm. The ultrasonic velocity is calculated by using relation,

$$\text{Ultrasonic velocity (U)} = \lambda \times \text{Frequency} \times 10^3 \quad \text{---------- (2)}$$

Some acoustical parameters have been calculated using the standard relations. The adiabatic compressibility (βs) of solvent and solution are calculated by using equations

$$\text{Adiabatic compressibility solution } (\beta s) = 100/ U^2 s \times ds \quad \text{---------- (3)}$$

$$\text{Adiabatic compressibility solvent } (\beta 0) = 100/ U^2_0 \times d_o \quad \text{---------- (4)}$$

$$\text{Acoustic impedance } (Z) = Us \times ds \quad \text{---------- (5)}$$

Where, U_0, d_0, β0 and Us, ds, βs are ultrasonic velocity, density and adiabatic compressibility of solvent and solution respectively.

$$\text{Intermolecular free length } (Lf) = K \times \sqrt{\beta s} \quad \text{---------- (6)}$$

$$\text{Relative association } (R_A) = (ds /d0) \times (U0 /Us)^{1/3} \quad \text{---------- (7)}$$

Where, K is Jacobson's constant[19] is calculated by using relation,

$$K= (93.875+0.375xT) \times 10\text{-}8 \quad \text{---------- (8)}$$

Where, T is temperature at which experiment is carried out.

Apparent molal compressibility (Øk) has been calculated by using the relation,

$$\beta s\, d0 - \beta 0\, ds = \beta s \times M$$

$$(Øk) = 1000 X \beta s\, d0 - \beta 0\, ds / m \times ds \times d0 + \beta s \times M/ ds \quad \text{---------- (9)}$$

Apparent molal Volume (Øv) has been calculated by using the relation,

$$M (d0 - ds) \times 1000 (Øv) = M/ds \; X \; (do\text{-}ds) \times 1000/mxdsxdo \quad \text{---------- (10)}$$

$$Øk(s) = Øk^0(s) + Sk_{(s)} \sqrt{m} \quad \text{---------- (11)}$$

$$Ø_v = Ø_v^o + Sv \sqrt{m} \quad \text{---------- (12)}$$

RESULT AND DISCUSSION

In the present investigation, different acoustical properties such as ultrasonic velocity (Us),density (ds), adiabatic compressibility (βs), intermolecular free length (Lf), specific acoustic impedance (Z), apparent molal volume (Øv), apparent molal compressibility(Øk(s)),

relative association (R_A) are listed in table. It is found that ultrasonic velocity decreases with decrease in percentage of dioxane The ultrasonic velocity is related to intermolecular free length. The variation of ultrasonic velocity in solution depends upon the increase or decrease of intermolecular free length after mixing the solute is based on a model for sound propagation proposed by Eyring and Kincaid[20]. The intermolecular free length (Lf) increases with increasing the percentage of dioxane, hence decrease in ultrasonic velocity with increasing the percentage of dioxane. This indicates that there is a weak interaction between ion and solvent molecules which suggesting a structure non-promoting behavior of the added solute. This also implies increase in number of free ions showing the occurrence of ionic dissociation due to weak ion-ion interactions.

The value of specific acoustic impedance (Z) decreases with decrease in the percentage of dioxane for given system. This is due to decrease in the strength of intermolecular attraction. The specific acoustic impedance (Z) is directly proportional to ultrasonic velocity and inversely proportional to adiabatic compressibility and shows similar behaviour to that of ultrasonic velocity and opposite to that of adiabatic compressibility. It was found that the value of adiabatic compressibility increases with decrease in percentage of dioxane indicates that there is weak solute-solvent interaction may be due to departure of solvent molecules around ions. The relative association is the property used to understand the interaction in solution. The relative association is measure of extent of association of the component in the mixture. The value of relative association decreases with decrease in percentage of Dioxane-water solvent.. This is due to the breaking up of the associated solvent molecules on addition of dioxane in it. It was observed that apparent molal volume decreases with decrease in percentage of Dioxane-water solvent the system. It indicates the existence of weak ion-solvent interaction.The apparent molal volume increases due to decreasing dielectric constant of medium with increase in percentage of Dioxane-water solvent.

The value of apparent molal compressibility decreases with decreases in percentage of Dioxane-water solvent for the system. The positive value of apparent molal compressibility shows the strong electrostatic attractive force in the vicinity of ions causing electrostatic solvation of ions

Table

Acoustic Properties of ligand (L) at different percentages in Dioxane-water Mixture

% of Dioxane	Us ($m.sec^{-1}$)	ds ($g.cm^{-3}$)	Bs (bar^{-1})	Lf (A^0)	Øv (cm^3mole^{-1})	$Ø_{k(s)}$ ($cm^3mole^{-1}bar^{-1}$)	R_A	Z ($cm.sec^{-1}.cm^{-3}$)
100	1630.22	0.9039	5.04×10^{-4}	13.51×10^2	1006.11	25.36	0.9176	14773.55
95	1584.30	0.9125	4.77×10^{-4}	13.14×10^2	900.18	15.92	0.9194	1467.57
90	1560.45	0.9275	4.52×10^{-4}	12.80×10^2	723.23	10.42	0.9285	1456.59
85	1544.15	0.9385	4.35×10^{-4}	12.56×10^2	595.86	6.92	0.9354	1449.18
80	1514.65	0.9481	4.20×10^{-4}	12.33×10^2	487.63	3.42	0.9410	1436.04
75	1480.85	0.9510	4.03×10^{-4}	12.08×10^2	455.46	1.09	0.9479	1408.28

CONCLUSION

The present study shows the experimental data for ultrasonic velocity, density at 30 ± 0.1^0C for synthesized Dibromo Chalcone in 70% Dioxane-water mixture. From experimental

data, the acoustical properties were calculated. The solute-solvent interaction and ion-ion / solute-solute interaction existing between Dibromo Chalcone ligand and different percentage of dioxane were also studied with the help of experimental data. Lastly it has been concluded from the experimental data, that the solute-solvent interaction in Dibromo Chalcone and dioxane systems are weak.

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8

Synthesis, Physicochemical evaluation of heteryl amino derivatives of bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(methylthio) pyrimidine] diazene

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Abstract:

Study of the synthesis and pharmacological evaluation of heteryl amino derivatives of bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(methylthio)pyrimidine]diazene,we obtained good result Antimycobacterium activity and Antityphoid activity.

Introduction:

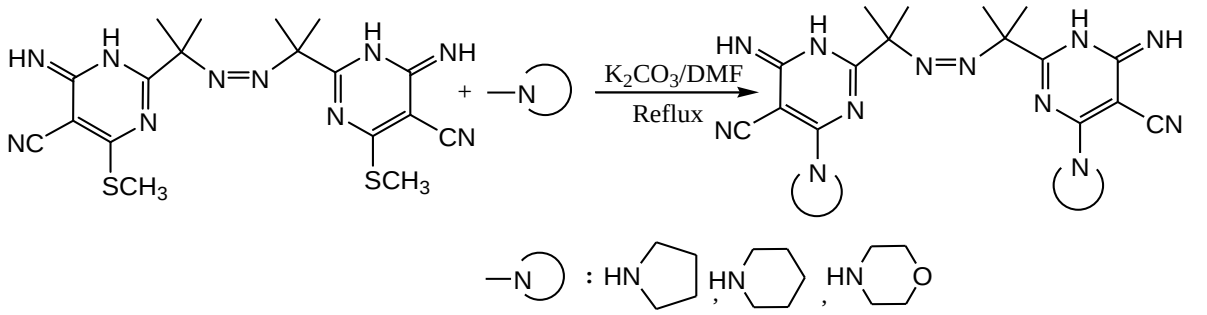
The understanding of principles of drug design and development of the drug molecules is important study the physicochemical properties of chemical compounds used to develop novel pharmacologically active compounds. The biological activities, mechanism of actions, possible biological activities of the metabolites and significance of stereochemistry for molecules are important factors for new drug design [1]. All these principles are based on the basic organic chemistry, physical chemistry and biochemistry. Heterocyclic compounds contain, one or more atoms of other elements apart from carbon, common hetero atoms are sulphur, nitrogen and oxygen [2]. The heterocyclic compounds having less common atoms such silicon, bromine, phosphorus, tin, boron are much investigated in recent years. The heterocycles with five or six atoms in the ring are the most important [3]. The practice of medicinal chemistry is devoted to the research in development of new diseasetreating agent. The process of finding a new drug is complex and involves talent of people from variety of disciplines [4]. The important aspect of medicinal chemistry is to establish a relationship between pharmacological activity and chemical structure [5].

Pyrimidine is a six membered cyclic compound containing 2 nitrogen and 4 carbon atoms which is pharmacologically inactive however its substituted derivatives shows an important place in modern medicine [6]. Pyridazine 1, oxygenated derivative-pyridazinone 2 and benzfused pyridazine or phthalazine 3 are heterocyclic compounds that contain two adjacent nitrogen atoms (1,2-diazine) in the ring structure [7]. They show a high range of pharmacological activities and are found in different natural compounds with different biological activities [8]. Many heterocyclic compounds obtained from synthetic as well as natural sources, generally in practice have one or more nitrogen in the heterocyclic ring system. Diazines (1,2/1,3/1,4) are important heterocylic rings. Recently, much attention has been focused on diazine derivatives for their broad-spectrum pharmacological activities [9].

Present Work:

The newly synthesised molecule possesses two methylthio groups which can be easily substituted with heteryl amines that can be marked.

Heteryl amino derivatives ofcan be prepared by reacting it with substituted heteryl amines in 1:2 proportion using DMF solvent and anhydrous K_2CO_3 catalyst to yield compounds .



Scheme: Synthesis of heteryl amino derivatives of bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(methylthio) pyrimidine] diazene

Results and Discussion:

In the study of optimization of reaction condition and solvent for the synthesis of heteryl amino derivatives of bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(methylthio) pyrimidine] diazene we have obtained low yield at room temperature than the reaction carried out at the reflux condition.

Experimental Section:

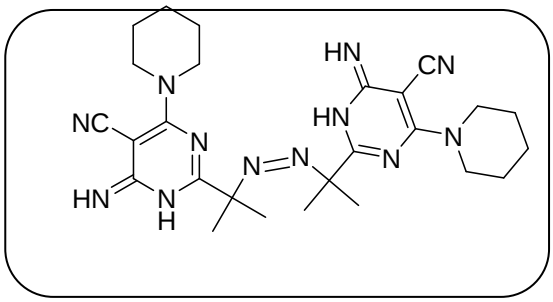
All chemicals procured from spectrochem, Alfa Aeser, SDfine, Sigma Aldrich were used without further purification. The IR spectra were recorded with Shimadzu FTIR. The melting points were recorded using Veego digital melting point apparatus. The NMR spectra were recorded with Bruker 400MHz using DMSOd6 solvent.

General Procedure:

Compound (0.442 g, 1 mmol) and different heteryl amines, (1 mmol) in 1:2 proportion using 15 ml of DMF as solvent and catalyst anhydrous K_2CO_3as catalyst (10 mg) reflux for 5-7 hours, the progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered off, washed many times with water and recrystallized from ethanol.

Spectral Data:

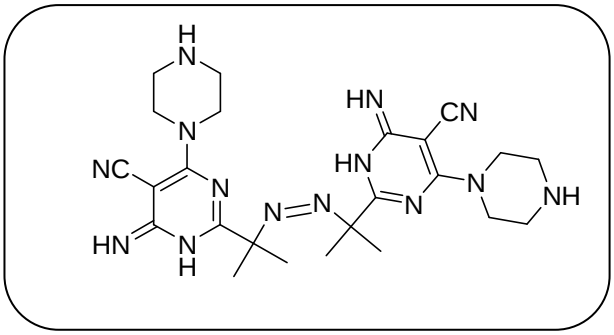
1) bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(piperidinyl) pyrimidine] diazene



- **Molecular Formula** : $C_{26}H_{36}N_{12}$
- **Mol. Weight (g/mol)** :516.6
- **IR(KBr) (cm^{-1})** : 3300(=NH), 2198 (CN), 1616 (C=N)
- **^{1}H NMR (δ, ppm) (DMSOd_6)** : 1.24 (q, 8H), 1.36 (s, 12H), 2.82 (t, 8H), 3.86 (s, 2H), 9.21(s, 2H)
- **Mass (m/z)** : 372.2, 516.4 ($M^{+\cdot}$)

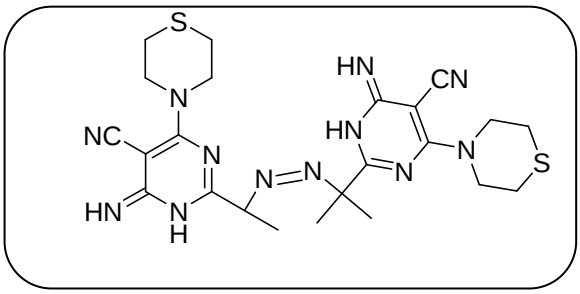
2) bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(p-piperazinyl) pyrimidine]

diazene



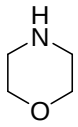
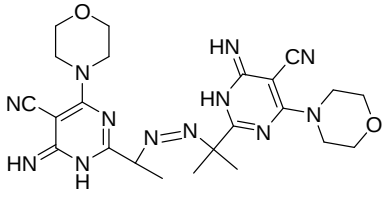
- **Molecular Formula** : $C_{24}H_{34}N_{14}$
- **Mol. Weight (g/mol)** :518.6
- **IR(KBr) (cm^{-1})** : 3309 (=NH), 2204 (CN), 1610 (C=N)
- **^{1}H NMR (δ, ppm) (DMSOd_6)** : 1.35 (s, 12H), 3.08 (t, 8H), 3.10 (t, 8H), 3.82 (s, 2H), 8.00 (s, 2H)
- **Mass (m/z)** : 332.6, 518.9($M^{+\cdot}$)

3) bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(4-thiomorpholino) pyrimidine] diazene



- **Molecular Formula** : $C_{24}H_{32}N_{12}S_2$
- **Mol. Weight (g/mol)**: 552.7
- **IR(KBr) (cm^{-1})** : 3301 (=NH), 2198 (CN), 1606 (C=N)
- **Mass (m/z)** : 477.1, 552.6 ($M^{+\cdot}$)

Table: Synthesis of heteryl amino derivatives of bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(methylthio) pyrimidine] diazene

Entry	Substrate	Product	Reaction Time (h)	Yield (%)	M.P. (^{0}C)
a			**5.0**	**74**	**194**

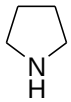
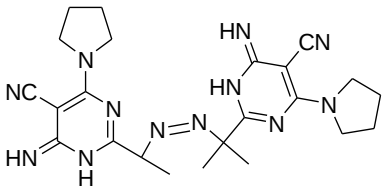
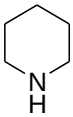
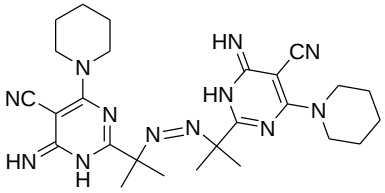
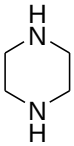
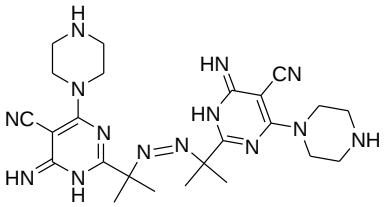
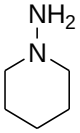
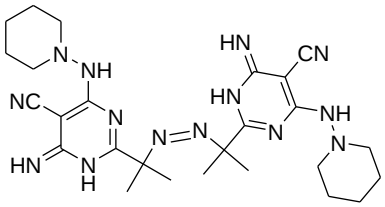
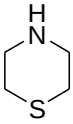
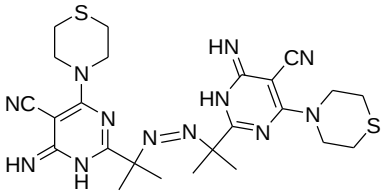
b			**5.5**	**70**	**186**
c			**6.5**	**67**	**180**
d			**4.5**	**78**	**203**
e			**5.0**	**79**	**178**
f			**6.5**	**83**	**182**

Table : Physicochemical evaluation of heteryl amino derivatives bis[5-cyano-1,6-dihydro-6-imino-2-isopropyl-4-(methylthio) pyrimidine] diazene
Solvent: DMSO

Sr. No.	Compound (0.1M)	Density (ρ) (g/cm^3)	Viscosity ($\mu*10^3$) poise	Refractive Index (n)
1	**3.19a**	0.9520	6.3465	1.5423
2	**3.19b**	0.9689	6.8745	1.5279
3	**3.19c**	0.9588	7.9472	1.5364
4	**3.19d**	0.9637	6.3120	1.5457
5	**3.19e**	0.9697	7.1857	1.5663
6	**3.19f**	0.9884	6.4412	1.4666

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9

Novel Synthesis and Characterization of Some Substituted Chlorosubstituted Aryl Substituted 1,3-Thiazole as Antibacterial Agents

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Abstract :- The synthesis, spectral analysis and biological activities of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one-2-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole ($8d_2$) (J") have been carried out. In this case 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(heptan-1-one)-2- amino-1,3-thiazole (8d) (J), 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one-2-[(2-hydroxy-3,5-dichlorophenyl) ethanonylamino]-1,3-thiazole ($8d_1$) (J') & 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one- 2-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole ($8d_2$) (J") have been screened. The compound (J) was synthesized from 1-(2'-Hydroxy-3',5'-dichlorophenyl)-2-bromo-1,3-nonanedione (a_4) by the action of thiourea, while (J") was synthesized from (J) by reaction with α-bromo, 2-hydroxy-3,5 dichloroacetophenone to get 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one-2-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole ($8d_1$) (J'). Further (J') on treatment with KSCN was dissolved in acetic acid gave (J''). The nanoparticles of the compounds J, J'and J'' have been prepared by using ultrasonic technique. The newly synthesized titled compound and it's nanoparticles were screened for their antibacterial activity against some pathogens ; Gram+ve bacteria viz. Staphylococcus pneumoniae, Staphylococcus aureus and Gram-ve bacteria viz. Escherichia coli and Pseudomonas fluorescens by using agar disc diffusion method.All the newly synthesized compounds were found to be active against test pathogens.

Keywords : Chalcone, thiazine, thiourea, α-bromo,2-hydroxy-3,5 dichloroacetophenone, KSCN was dissolved in acetic acid, antibacterial assay.

INTRODUCTION : Heterocyclic nucleus plays an important role in medicinal chemistry and it is a key template for the growth of various therapeutic agents. Thiazole is a heterocyclic compound featuring both a nitrogen atom and sulfur atom as part of the aromatic five-membered ring. Thiazoles and related compounds are called1,3-azoles (nitrogen and one other hetero atom in a five-membered ring). They are isomeric with the 1,2-azoles, the nitrogen and sulphur containing compound being called isothiazoles. Thiazoles are found naturally in the essential vitamins. Molecules that possess sulfur atoms are important in living organisms. Chalcones and their analogues having α, β-unsaturated carbonyl system are very versatile substrates for the evolution of various reactions and physiologically active compounds. Plant Pathology or Phytopathology deals with the cause, etiology, resulting losses and control or management of the plant diseases.

. It is the scientific study of diseases in plants caused by pathogens (infectious organisms) and environmental conditions (physiological factors). Organisms that cause infectious disease include *fungi*, *oomycetes*, *bacteria*, *viruses*,*phytoplasmas*, *protozoa*, *nematod-es* and *parasitic plants*.

The researchers[1-6] have reported the synthesis of several thiazoles and also their potent biological activities such as antimicrobial[7], antibacterial[8], antifungal[9], fungicidal[10] and

insecticidal agent[11].

Now a days nanotechnology is a promising field of interdisciplinary research. It opens up a wide array of opportunities in various fields like medicine, pharmaceuticals, electronics and agriculture. Since the physiochemical properties of nanoforms vary greatly, it becomes important to examine the effect of nanoparticles on microorganisms to harness the benefit of this technology in the plant protection especially against phytopathogens. Previous studies confirmed that metal nanoparticles are effective against pathogens, insects and pests. Hence nanoparticles can be used in the preparation of new formulations like nanomedicines for the diseases like diagnosing & treating cancer[12], enhancing outer membrane of living cells[13], inhibiting tumour growth in human being[14], brain cancer [15]. Nanotechnology has the potential to revolutionize the different sectors of agriculture and food industry with modern tools for the treatment of diseases by providing the medicines for rapid diseases like malaria[16], cancer & HIV[17], breast cancer[18], localized diseases[19].

In the present study, the chlorosubstituted 1,3-thiazole & their imidazole derivatives (J") have been prepared along with their nanoparticles and screened them for their antibacterial activities against some Gram+ve bacteria viz. Staphylococcus pneumoniae, Staphylococcus aureus and Gram-ve bacteria viz. Escherichia coli and Pseudomonas. All the newly synthesized compounds were found to be active against test pathogens.

EXPERIMENTAL :-

All the glasswares used in the present work were of pyrex quality. Melting points were determined in hot paraffin bath and are uncorrected. The purity of compounds was monitored on silica gel coated TLC plate. IR spectra were recorded on Perkin-Elmer spectrophotometer in KBr pelletes, H^1 NMR spectra on spectrophotometer in $CDCl_3$ with TMS as internal standard. UV spectra were recorded in nujol medium. The analytical data of the titled compounds was highly satisfactory. All the chemicals used were of analytical grade. All the solvents used were purified by standard methods. Physical characterisation data of all the compounds is given in Table 1.

2'-Hydroxy 3,5'-Dichloroacetophenone:

2-Hydroxy-5-chloroacetophenone was dissolved in acetic acid (5 ml), Sodium acetate (3g) was added to the reaction mixture and then chlorine in acetic acid reagent (40 ml; 7.5 w/v) was added dropwise with stirring. The temperature of the reaction mixture was maintained below 20^0C. The mixture was allowed to stand for 30 minutes. It was poured into cold water with stirring. A pale yellow solid then obtained was filtered, dried and crystallized from ethanol to get the compound 2'-hydroxy 3',5'-dichloroacetophenone.

Preparation of 2'-hydroxy-3',5'-dichloro-4-hexylchalcone :

2-Hydroxy-3,5-dichloroacetophenone (0.01 mol) dissolved in ethanol (50 ml) treated with heptanaldehyde (0.1 M) at its boiling temperature. Aqueous sodium hydroxide solution [40%, 40 ml] was added dropwise and the the mixture was stirred mechanically at room temperature for about 1 hour. It is then kept for 6 to 8 hours followed by decomposition with ice cold HCl [1:1]. The yellow granules thus obtained were filtered, washed with 10% $NaHCO_3$ solution and finally crystallized from ethanol-acetic acid solvent mixture to get the compound .

Preparation of 1-(2'-hydroxy-3'-5'-dichlorophenyl)-2,3-dibromononan-1-one (a_1) :

2'-Hydroxy-3',5'-dichloro-4-hexylchalcone (0.01 M) was suspended in bromine–

glacial acid reagent [25% w/v] [6.4 ml]. The reagent was added dropwise with constant stirring. After complete addition of reagent the reaction mixture was kept at room temperature for about 30 minutes. The solid product, thus separated, was filtered and washed with a little petroleum ether to get the compound (a_1).

Preparation of 2-(4"-hexyl)- 6,8-dichloroflavone (a_2):

1-(2'-Hydroxy-3',5'-dichlorophenyl)-2,3-dibromo-nonan-1-one (0.01 mol) was dissolved in ethanol (25 ml). To this, aqueous solution of KOH (25 ml) was added. The reaction mixture was refluxed for 1 hour, cooled and diluted with water. The product, thus separated, was filtered and crystallized from ethanol to get the compound (a_2).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-1,3-nonanedione (a_3) :

2-(4"-Hexyl)-6,8-dichloroflavone (0.01 mol) was dissolved in ethanol (25 ml). To this, aqueous solution of HCl (25 ml) was added. The reaction mixture was then refluxed for one hour, cooled and diluted with water. The solid product, thus obtained, filtered and crystallized from ethanol to get the compound (a_3).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-2-bromo-1,3-nonanedione (a_4) :

1-(2'-Hydroxy-3',5'-dichlorophenyl)-1,3-nonanedione (0.01 mol) was dissolved in a mixture of ethanol (10 ml) and dioxane (10 ml). To this, calculated amount of liquid bromine (0.5 ml) was added. The product was not separated even after standing for one hour. It was then diluted with water and washed with water several times and extracted with ether. The solvent was removed under reduced pressure to get the white solid of the compound (a_4).

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(heptan-1-one)-2- amino-1,3-thiazole (J) :

1-(2'-Hydroxy-3',5'-dichlorophenyl)-2-bromo-1,3-nonanedione (a_4) (0.01 mol) and thiourea (0.01 mol) were dissolved in ethanol (25 ml). To this, aqueous KOH solution (0.01 mol) was added. The reaction mixture was then refluxed for three hours, cooled, diluted with water and acidified with conc HCl. The product, thus separated, was filtered and crystallized from ethanol to get the compound (J).

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one-2-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole (J'):

A stoichiometeric mixture of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(heptan-1-one)-2- amino-1,3-thiazole (J) and α-bromo-2-hydroxy-3,5-dichloro acetophenone was dissolved in ethanol and refluxed for one hour. It was then cooled, diluted with water and crystallized from ethanol to get the compound (J').

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one- 2-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole (J"):

A stoichiometeric mixture of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one-2-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole(J') and KSCN was dissolved in acetic acid, refluxed for 4.5 hours, cooled ,diluted with water,and solid product, thus obtained crystallized from ethanol to get the compound (J")**.**

The UV, IR, and NMR spectral data :-

Compound (J) :

UV : Spectrum No. 1

The UV-Vis spectrum of the compound (J) reported in dioxane showed λ_{max} value 410 nm corresponding to $n \rightarrow \pi^*$ transition.

IR (KBr) :- Spectrum No. 2
3036.60 cm^{-1} (-OH phenolic), 2955.55cm^{-1} (aliphatic -C-H stretching), 3036.60cm^{-1} (aromatic -C-H stretching), 3797.72 cm^{-1} (-NH_2 stretching), 1538.48 cm^{-1} (-C=N stretching), 1228.56 cm^{-1} [(C-N=) stretching], 756.57 cm^{-1} (C-Cl stretching in aliphatic), 1073.66 cm^{-1} (C-Cl) stretching in aromatic).

PMR :- Spectrum No. 3
∂ 5.2 (hump, 2H, -N-**H_2**) ; ∂ 6.7 (d, 1H, -CH=C-**H**) ; ∂ 6.8 (d, 1H, -C**H**=C-H) ; ∂ 7 to 7.8 (m, 6H, Ar-**H**) ; offset (region not observed, observed, O-**H**)

Compound (J'') :

UV : Spectrum No. 4
The UV-Vis spectrum of the compound J" reported in dioxane showed λ_{max} value 399 nm corresponding to $n \rightarrow \pi*$ transition.

IR (KBr) :- Spectrum No. 5
1649 cm^{-1} (=C=O stretching), 3391 cm^{-1} (-OH phenolic), 2925 cm^{-1} (aliphatic -C-H stretching), 3068 cm^{-1} (aromatic -C-H stretching), 1435.8 cm^{-1} (-C=N stretching), 1305 cm^{-1} [(C-N) (C-NO_2) stretching], 738 cm^{-1} (C-Cl stretching in aliphatic), 2547 cm^{-1} (-S-H stretching).

1.02

PMR :- Spectrum No. 6

∂ 7.4 to 8.25 (m, 4H, Ar-**H**) ; ∂ 0.80 (t, 3H, -CH2-C**H**3**,** ∂ 1.064 (envelope of CH2, **10H,** -(CH2)-C**H3).**

Preparation of Nanoparticles of the Titled Compound:

Ultrasonic Processor Sonapros PR-250MP was used to produce nanoparticles of the test compound. The test compound was dissolved in dioxane to prepare 0.1 M solutions. This solution was taken in a beaker and the probe of the sonapras 250 MP was dipped in solution. These solution was exposed to sonopros MP 250 for 10 minutes separately. The test compound was converted to nanoparticles. The solvent dioxane was evaporated by conventional heating method. The size of nanoparticles of the test compound was confirmed by X-ray diffraction studies using Benchtop x-ray diffraction (XRD) instrument **(**Miniflex).

The thin film of the nanoparticles of the test compound was prepared on glass slide. This slide was intr oduced to the X-ray diffraction instrument to get graphical information which was used for the calculation of the crystal size of test compounds.

Characterisation of Size of Nanoparticles of the Test Compound:

The crystal size of nanoparticles of the test compound is calculated by using Debye - Scherrer equation.

$$D = \frac{0.94\,\lambda}{\beta . \cos\theta}$$

Where,

D = The average crystalline size.

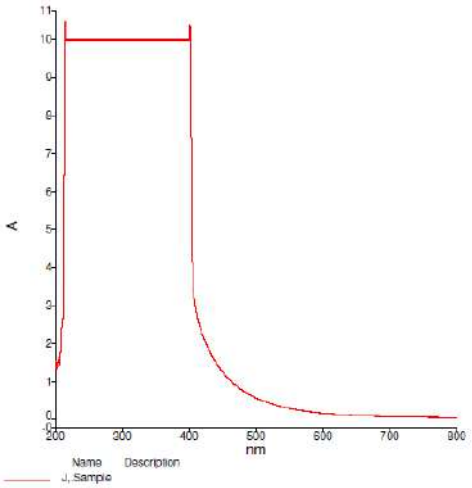
0.94 = The particle shape factor which depends on the shape and size of the particle.

λ = is the wavelength.

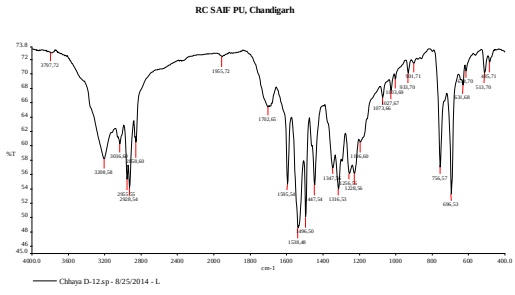
□ = is the full width at half maximum [FWHM] of the selected diffraction peaks (β = 0.545)

□ = is the Bragg's angle obta ined from 2θ va lues which was corresponding to the maximum intensity peak

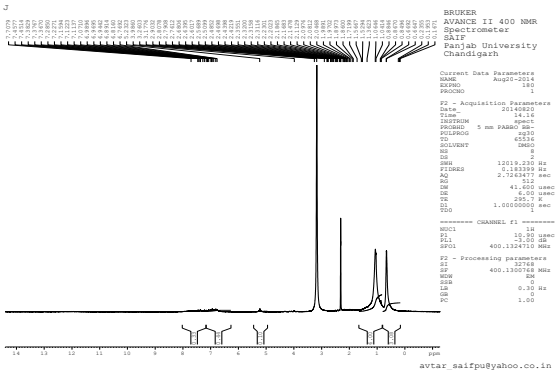
in XRD pattern (□ = 0.7501 rad).



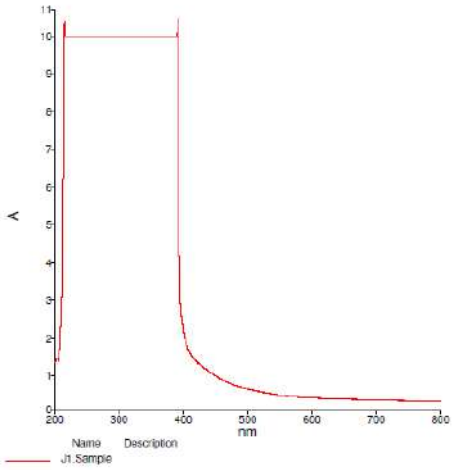
Spectrum No. 01



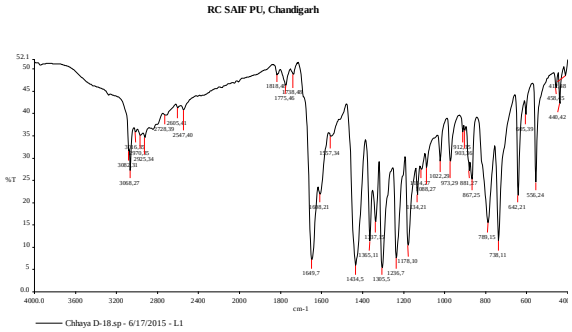
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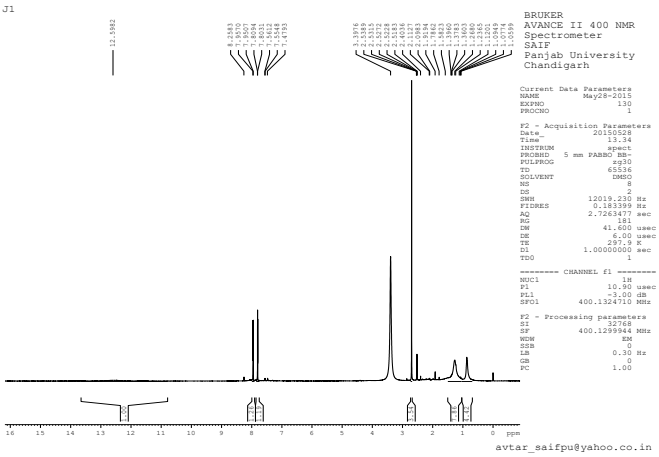
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Spectrum No. 04



Spectrum No. 05

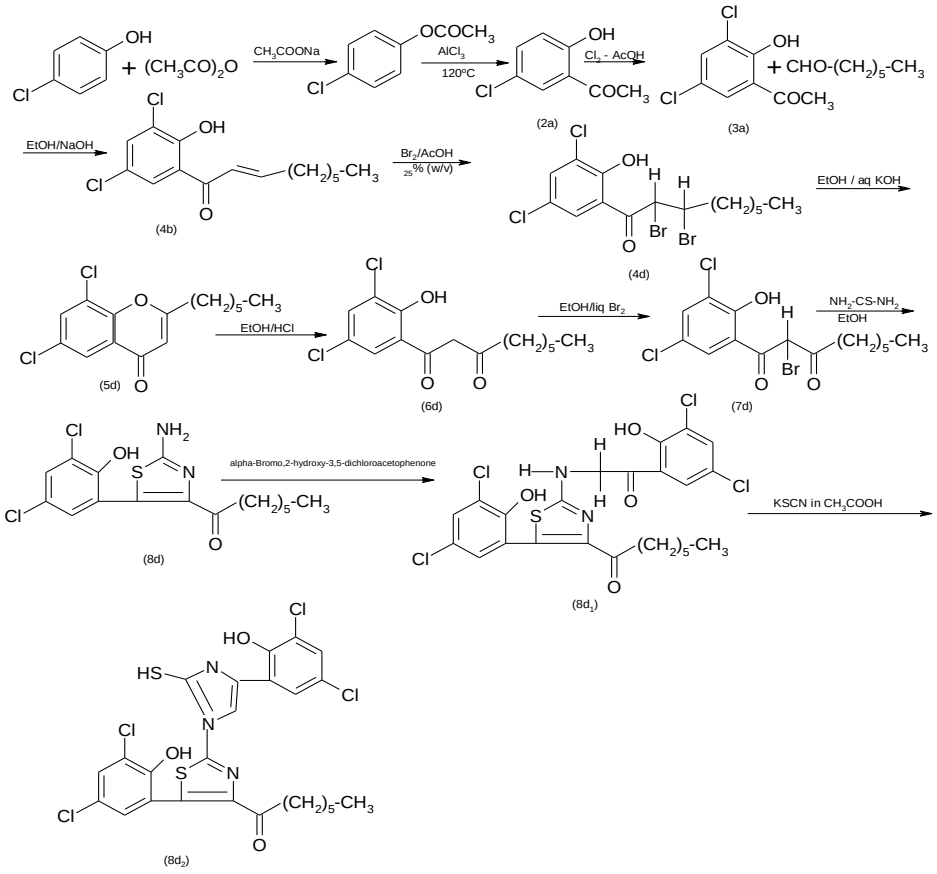


Spectrum No. 06

Table 1 : Characterisation data of newly synthesized compounds :

Compounds	Molecular formula	M.P. in ^{0}C	% of yield	% of element					
				C	H	N	S	Cl	Br
	$C_8H_6O_2Cl_2$	54	80	47.90/48	2.95/3			34.15/34.58	
a	$C_{15}H_9O_4NCl_2$	250	70	53.10/53.25	2.40/2.66	3.98/4.18		21/21.77	
a_1	$C_{15}H_9O_4NCl_2Br_2$	72	70	36.01/36.14	1.78/1.80	2.78/2.81		14.20/14.25	32.08/32.12
a_2	$C_{15}H_7O_4NCl_2$	132	60	53.14/53.57	2.07/2.08	4.13/4.16		21.03/21.13	
a_3	$C_{15}H_9O_5NCl_2$	117	50	50.74/50.84	2.45/2.54	3.90/3.95		20.03/20.05	
a_4	$C_{15}H_8O_5NCl_2Br$	78	60	41.12/41.57	1.78/1.84	3.20/3.23		16.08/16.39	18.34/18.47
J	$C_{16}H_{20}O_2N_2Cl_2S$	96	60	51.10/51.20	5.30/5.33	7.40/7.46	7.67/7.76	17.20/17.23	
J’	$C_{24}H_{22}O_4N_2Cl_4S$	94	70	49.85/50.00	3.78/3.81	4.78/4.86	5.50/5.55	24.50/24.65	
J”	$C_{25}H_{21}O_3N_3Cl_4S_2$	108	70	48.60/48.62	3.38/3.40	6.75/6.80	10.35/10.37	23.00/23.01	

Scheme :



(2a) (3a) (4b) (4d) (5d) (6d) (7d) (8d) (8d1) (8d2)

Where :

1) R_1 = -H, -C_6H_5
2) R_2 = -H, -C_6H_5

EXPERIMENTAL DETAILS AND DISCUSSION OF RESULTS :

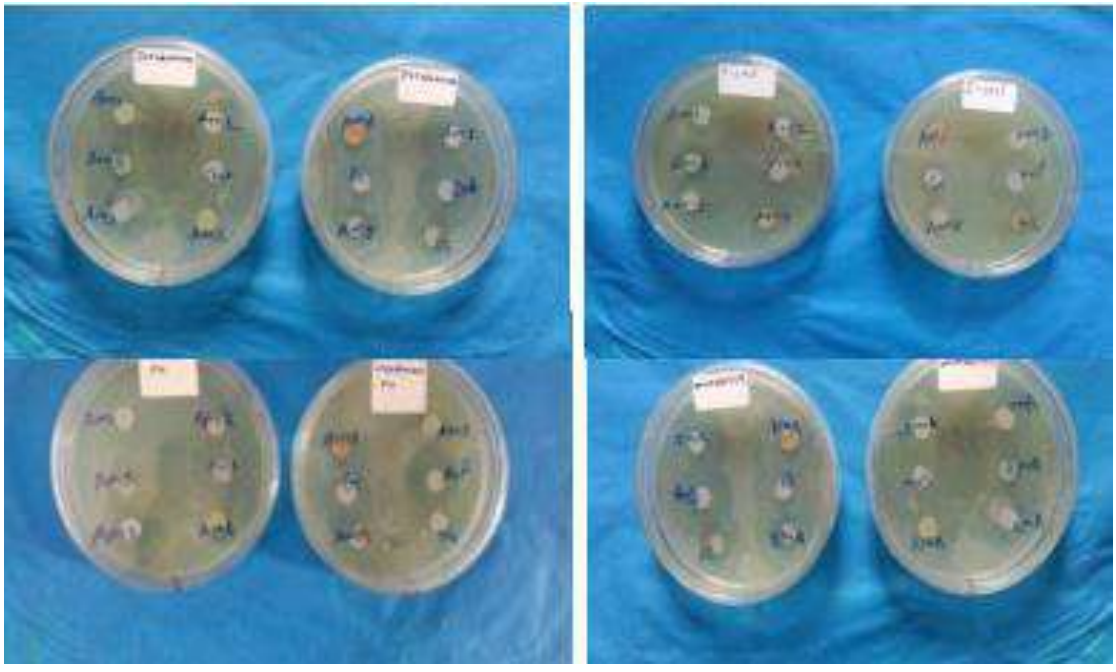
Antibacterial Assay :

The compounds (a – J") were screened for their antibacterial activity against Gram +ve bacteria viz. Staphylococcus pneumoniae, Staphylococcus aureus and Gram -ve bacteria viz. Escherichia coli and Pseudomonas fluorescens at conc. of 1000 ppm by using Agar disc diffusion method. Ofloxacin used as a standard and chloroform as solvent control. The zones of inhibition formed were measured in mm and are shown in Table No.2.

Table No.2- Impact of test compounds against plant pathogens :

Sample Code	(Gram positive)		(Gram Negative)	
	Staphylococcus pneumoniae	Staphylococcus aureus	Escherichia coli	Pseudomonas fluorescens
a	**-**	**15**	**12**	**12**
a_1	**-**	**13**	**-**	**12**
a_2	**17**	**14**	**12**	**15**
a_3	**15**	**-**	**12**	**25**
a_4	**14**	**12**	**15**	**12**
J	**14**	**15**	**15**	**-**
J'	**12**	**13**	**12**	**18**
J"	**12**	**-**	**14**	**25**
Reference Antibiotic	(Ofloxacin)	(Ofloxacin)	(Ofloxacin)	(Ofloxacin)

Diameter of inhibition zone (mm)



RESULT AND DISCUSSION :

Most of the test compounds have shown remarkable and very encouraging antibacterial activities. A further detailed study in the light of plant pathology is advised.

ACKNOWLEDGEMENTS :

The authors are thankful to Dr.D.H.Pundkar, Principal, Dr.Manorama & Prof.H. S.Pundkar, Arts, Commerce & Science College, Balapur, Dr.B.B.Wankhade, Principal, Malkapur Vidnyan Mahavidyalaya, Malkapur, and Shri Shankarlal Khandelwal College, Akola for providing help in carrying out the antibacterial activities & for providing necessary facilities to carry out the research work.

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10

Mini Review on biological aspects of 1,3,4-Thiadiazoles

Mr. N.D. Dahake*, Dr. V.H. Masand

Abstract: Thiadiazols are a significant class of heterocyclic compounds with a wide range of uses in biological, pharmacological, and chemical synthesis. They are also well-known for their benefits as metal chelating agents, cyanine dyes, oxidation inhibitors, and anti-corrosion agents. Researchers from all around the world are working on this moiety because of its wide range of uses, which has helped to enhance the chemistry of thiadiazols. The most recent information on advancements, novel approaches, synthetic strategies, methods used for thiadiazole synthesis, and their various medicinal uses, as well as the structure-activity relationship of the most effective compounds and their physical characteristics, is provided in this review article. For medicinal and organic chemists working on developing newer compounds with thiadiazole moiety that may be safer and more effective agents, this article can be a valuable resource.

Key words: Semi carbazide, thiadiazole, antitumour, antioxidant, anti-inflammatory.

Antibiotic Activity: It has been found that 1,3,4-thiadiazoles have a wide range of antibacterial activity. Through its several reactivity sites, which have been outlined above, the thiadiazole ring frequently served as a framework to which various pharmacophore compounds with comparable antibacterial properties were connected. Quinoline, pyrazole, triazole, piperine, imidazoline, and other well-known pharmacophore agents were known to exhibit a range of bioactivities (Schem – 1). In order to test the in vitro antibacterial activity of 2,8-substituted quinolin-1,3,4-thiadiazoleyl acetamide derivatives against Staphylococcus aureus, Streptococcus pyogenes, Salmonella typhimurium, and Escherichia coli, Bhat et al.Compounds 183 and 184 demonstrated superior inhibitory effects against S. aureus at MIC = 16 μg/mL (controlled to amoxicillin MIC = 32 μg/mL), while compounds 185 and 186 demonstrated superior outcomes against pyogenes at MIC = 16 μg/mL (controlled to amoxicillin MIC = 32 μg/mL).

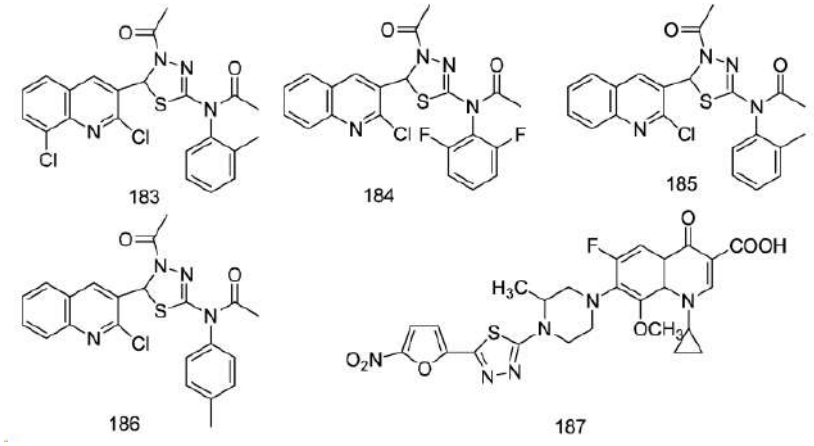


Figure 4- Scheme -1

Antiviral Activity: Research on 1,3,4-thiadiazoles' antiviral efficacy was unsatisfactory. Despite their best efforts, the majority of the time the researchers only saw moderate or even lower activity. Triazolo 1,2,4-[3,4-b]In vitro anti-HIV-1 (IIIB) and HIV-2 (ROD) activity in MT-4 cells was significantly lower with -1,3,4-thiadiazoles with 3,6-substituted by substituted phenyl, heterocyclic groups such as furan, thiophene, pyrozine, pyridine, pyrrole, coumarin, etc., adamantyl and acyclic C-nucleosides (compound

214) than the reference drug (Scheme 2). Moreover, 2-arylthioacetamino-1,3,4-thiadiazoles were produced and assessed for their ability to block HIV-1 reverse transcriptase as non-nucleoside inhibitors (NNRTIs) through an allosteric interaction with the non-nucleoside inhibitor binding site, or NNBS, which is a location next to the NRTI binding site. The new 1,3,4-thiadiazole compounds did not perform as well as their benzoimidazole analogues and the reference drug zidovudine, despite the fact that the nitrogen atom and the amino group of thiadiazole can form H bonds with the RT NNBS residues and the 5-position substituent can also contribute to the interaction with NNBS observed through docking simulation. Comparing thiadiazole compounds to their benzoimidazole equivalents and the reference medication zidovudine, they did not perform as well.

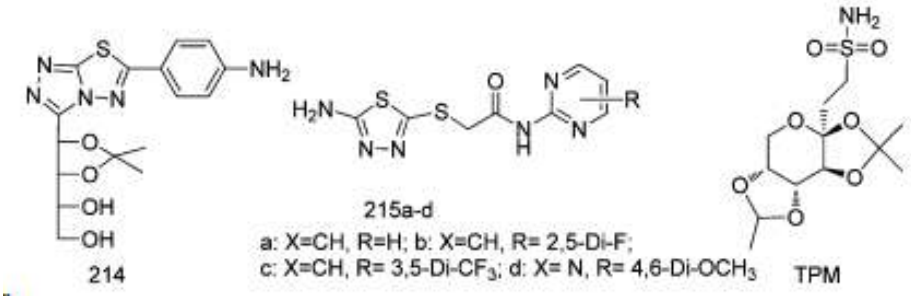


Figure 5 - Antiviral Analogues of 1,3,4-Thiadiazole

Antioxidant Activity: Antioxidants can stop chain reactions that could harm or kill a cell by removing free radical intermediates from oxidation events. Usually, they are reducing agents like polyphenols, ascorbic acid, or thiols. Similar to chemical antioxidants, a network of interacting antioxidant enzymes, including catalase, peroxiredoxins, thioredoxin and glutathione systems, superoxide dismutase (SODs), and catalase, protects cells from oxidative stress. There is a lot of literature on the antioxidant properties of 1,3,4-thiadiazoles. Compared to the reference antioxidant propyl gallate, N-(2,4-Dimethylphenyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine exhibited more superoxide anion scavenging action. The presence of a potent electron-withdrawing group (NO2) may be responsible for stabilising the negatively charged adduct that superoxide forms. This outcome supported the report by Chidananda. Notwithstanding the unsurprising results, some (benzo)-imidazothiadiazoles and triazolothiadiazoles demonstrated potential antioxidant activities against a variety of in vitro systems, including superoxide radical, 2,2-diphenyl-1-picrylhydrazyl DPPH radical, microsomal NADPH-dependent inhibition of lipid peroxidation LP levels, nitric oxide scavenging activity, and microsomal ethoxy resorufin O-deethylase (EROD). When used to scavenge free radicals (DPPH•, ABTS•+, and •OH) in vitro, thiol and aminothiol compounds formed from 1,3,4-thiadiazoles have been shown to have much greater antioxidant properties than their comparable analogues derived from benzothiazoles, with thiols being superior to aminothiols In comparison to the radioprotectors WR-2721 and WR-1065, analogue provided 83% protection against 2-deoxyribose degradation by •OH at 60 μM, scavenging DPPH• and ABTS•+ free radicals with IC50 values of 0.053 and 0.023 mM, respectively. However, in vivo tests revealed that benzothiazoles had a more effective radioprotective effect. It was proposed that there is a direct connection between the aromatic ring's ability to trap radicals and the thiol function's ability to capture them. Furthermore, studies in the literature have shown that 1,3,4-thiadiazoles had less antioxidant activity than oxadiazole units in both nitric oxide and DPPH techniques.61a,b The mutagenicity effect of cyclophosphamide was able to be mitigated by melatonin, the pineal gland indole, and its thiadiazol indole derivatives. This reduction in mutagenicity effect may have been caused by the antioxidant activity of these compounds in male mice. Additionally, the thiadiazole ring's existence was unable to interfere with its action.

Melatonin activity, however, was not affected by the mere existence of a thiadiazole ring fused to a melatonin moiety with an acetonitrile side chain.

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11

Simultaneous Non-aqueous Conductometric Investigation of Pharmaceutically Potent Ibuprofen-Paracetamol Combination Drugs

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Abstract

Simultaneous non-aqueous conductometric investigation of pharmaceutically potent ibuprofen-paracetamol combination drugs has been accomplished using the solvent isopropanol and the titrant KOH in isopropanol. Drugs ibuprofen and paracetamol are distinctly acidic in nature. These drug combinations are extensively used in medicines and pharmaceuticals. In present work, ibuprofen-paracetamol combination drugs are simultaneously investigated by non-aqueous conductometric titration method using the dip type of glass conductivity cell. This method has been found to be precise for assay of combination drugs and can be used even in common laboratories. The results are compared to those obtained by Indian Pharmacopoeia (IP) method.

Keywords : Non-aqueous, conductometric investigation, ibuprofen-paracetamol

Introduction

The literature survey showed that, different pharmaceutical drugs and organic compounds have been analyzed by the conductometric method[1-3]. Good amount of literature is available on determination of pharmaceutical compounds by acid-base titration method in non-aqueous solvents as well as other methods. Procedures for non-aqueous titrations are described in the main pharmacopoeias[4-6]. Conductometric titration method using conductivity cell is also recommended by the pharmacopoeias. Determination of pharmaceutical compounds by non-aqueous titration method is discussed and reviewed by many authors[7-9]. In the literature, different methods are given for the determination of ibuprofen[10,11]. Non-aqueous conductometric estimation of ibuprofen in perchloric acid has been reported earlier[12]. For the determination of combination drugs, different methods have been suggested and these are mostly concerns with the separation of components followed by individual component estimation using suitable technique. Investigation of pharmaceutically potent ibuprofen-paracetamol combination drugs by conductometric titration method using solvent isopropanol was not yet reported in literature. As the drugs ibuprofen and paracetamol are distinctly acidic in nature, could not be titrated directly with aqueous alkali because of their hydrolysis. The basic titrants are superior to the alkoxide solvents. These are more susceptible to the atmospheric moisture and carbondioxide.

Herein, the easy method to investigate the pharmaceutically potent drugs is reported. It will help in the investigation of raw materials and products for quick check of spurious drugs that are feared to penetrate the markets. In the reported work, conductometric titrations in non-aqueous medium using the solvent isopropanol and titrant KOH in isopropanol were carried out to analyze the ibuprofen and paracetamol in two component combination drugs without any separation.

Material and Methods

All the titrations were performed by a digital conductometer (Systronics-304) with dip type of glass conductivity cell having outer diameter of 15 mm and cell constant 1. Conductivity cell was conditioned in the desired solvent for 24 hours before the use. Conductometric titrations were carried out at constant temperature using thermostatic bath and the volume of titration solution was always kept constant (20 ml). Suitable volume corrections

were applied whenever necessary. Weightings of required drugs and chemicals were made on Contech, CAH-123 (±0.001 g) balance. Chemicals and solvents used were AR grade. Solvents were purified and made anhydrous by standard methods[13] and titrants were protected from atmospheric moisture and CO_2. Drugs used in present work were obtained from pharmaceutical laboratories. These are pharmaceutical in nature and included in pharmacopoeias[4-6].

Ten tablets of the same batch of ibuprofen-paracetamol drugs were accurately weighed and powdered for the present investigation. As per the requirement, quantity of powder equivalent to about 400 mg of ibuprofen and 325 mg of paracetamol was weighed accurately, treated with 50 ml of isopropanol and stirred vigorously for dissolving the active component of the tablets. Binding agents and fillers remained insoluble. Common additives present in the tablets i.e. calcium carbonate, glucose, lactose, starch, gum etc. were mostly insoluble in isopropanol. Solutions were filtered, residues were washed with small portions of isopropanol for three to four times and volumes of solutions were made to 100 ml with isopropanol. Aliquots of 10 ml of these solutions were diluted to 20 ml with isopropanol and titrated with 0.1 M solution of KOH in isopropanol by conductometric method using a conductivity cell. Conductometrically, titrant was standardized with 0.1 M benzoic acid in isopropanol. End points were found out by plotting the graphs and later on amount of drugs present in titrated weights of tablet powder were calculated. Amount of active components (drugs) present in one tablet was calculated from the average weight of the tablet. Same tablets were also analyzed by the method given in pharmacopoeias so as to compare the results.

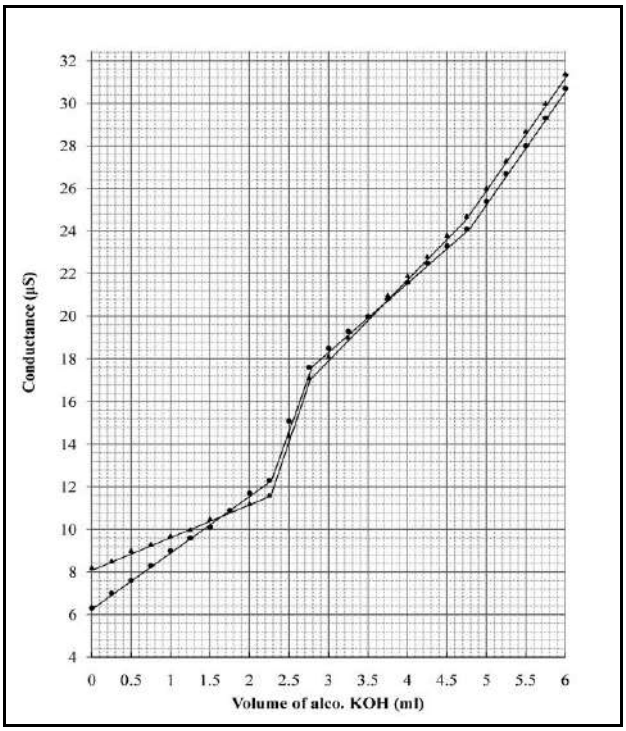
Results and Discussion

Ten tablets of the same batch of drugs ibuprofen and paracetamol were weighed and powdered. Powder equivalent to 400 mg of ibuprofen and 325 mg of paracetamol was exactly weighed, extracted with isopropanol and volume was made to 100 ml. The 10 ml of this solution was diluted to 20 ml with isopropanol and titrated conductometrically with KOH in isopropanol. Standardization of titrant was done using standard benzoic acid in isopropanol by conductometric titration. Weight of drugs ibuprofen and paracetamol in titrated amount of tablets was calculated. Investigation of same tablets was done by IP method and result for two tablets of different brands was tabulated. It was observed that, the reported method of non-aqueous conductometric titration gives quite accurate and comparable results to those obtained by IP method (**Table-1**). It is simple, precise and free from indicator error or interferences. Acidic drugs get hydrolyzed in presence of aqueous alkali, but in non-aqueous medium it can be avoided. As per the US Pharmacopoeia, alcoholic solution of the acidic drugs is to be titrated with aqueous alkali and such titration must be performed very fastly for minimizing the hydrolysis. Present method has not this limitation. The most common additives present in the tablets i.e. calcium carbonate, sugars, gum etc. are insoluble in isopropanol and do not affect the results. Conductometric breaks obtained using isopropanol as solvent are quite pronounced and prominent with minimum error (**Graph-1**). At the end point, solvent isopropanol permitted a large change in the concentration of solvated proton. Solvent isopropanol can be purified and made anhydrous very easily. Its dielectric constant is smaller. Present method is simple than other one, where the components are separated and investigated by spectrophotometric, chromatographic or other techniques.

Table-1 : Conductometric investigation of ibuprofen-paracetamol combination drugs

Sample	Label Claim (mg)		Weight Found by IP method (mg)		Weight Found by present method (mg)	
	Ibuprofen	Paracetamol	Ibuprofen	Paracetamol	Ibuprofen	Paracetamol
DT-01	400	325	398.80	326.80	399.10	327.50
DT-02	400	325	401.90	317.10	402.60	319.70

Graph-1 : Conductometric investigation of ibuprofen-paracetamol combination drugs



Conclusion

Simultaneous non-aqueous conductometric investigation of pharmaceutically potent ibuprofen-paracetamol combination drugs is fast, simple, precise method. It can be worked out in all common laboratories without the use of any kind of sophisticated equipments. For titration of drugs in non-aqueous medium, solvent isopropanol was found to be good one with accurate results. KOH in isopropanol was found to be better basic titrant to the alkoxide solvents that are susceptible to atmospheric moisture and carbondioxide.

Acknowledgement

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12

Cp*Co(III) Catalyzed Redox-Neutral Annulation: A Powerful Tool for Isoquinoline Synthesis from *N*-Cbz Hydrazones

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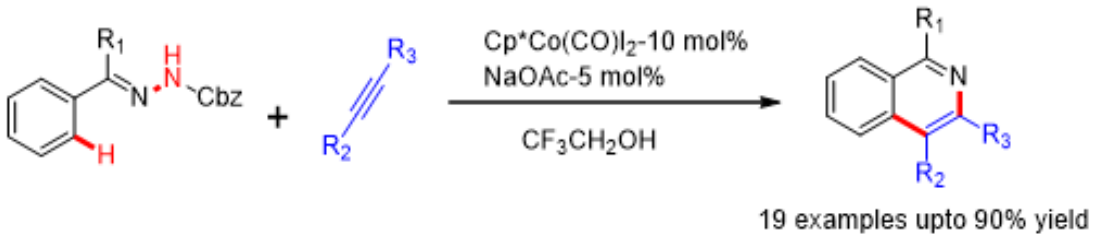
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Abstract

A new cascade oxidative cyclization reaction of *N*-Cbz hydrazones with internal alkynes has been explored for the preparation of isoquinoline derivatives using Cp*CoIII-catalyst via C-H and N-N bond functionalization. *N*-Cbz hydrazones are rarely explored as directing group for redox-neutral [4+2] cyclization reaction through the cyclometallation and this catalyst system does not require any external oxidizing agent as well as silver or antimony salt. The demonstrated efficient approach has been utilized for the synthesis of different isoquinoline derivatives with good regioselectivity and yields.

Introduction

Transition metal-catalyzed C-H bond functionalization is vital for modifying organic molecules, particularly in drug synthesis and green chemistry. Current efforts are directed at enhancing Cp*Co(CO)I2-catalyzed C-H bond activation with first-row transition metals [1-5]. Isoquinoline derivatives, essential for diverse pharmacological applications and as catalyst ligands, are employed in materials, dye, and paint industries using various name reactions. In recent decades, C-H bond activation has become a pivotal pathway for achieving high yields in isoquinoline derivative synthesis [6-12].



Scheme 1. Transition metal catalyzed annulation reaction for the synthesis of isoquinoline.

Exploring transition metal-catalyzed isoquinoline synthesis has faced challenges like external oxidant requirements, expensive catalysts, and limited starting materials. Addressing these issues, the Zhu group showcased the use of the affordable cobalt catalyst for C-H/N-N bond activations. [13–17]. Challenges in existing protocols, such as the use of air and silver salt, highlight the need for a cost-effective Co-catalyzed synthetic protocol without external oxidants [18].

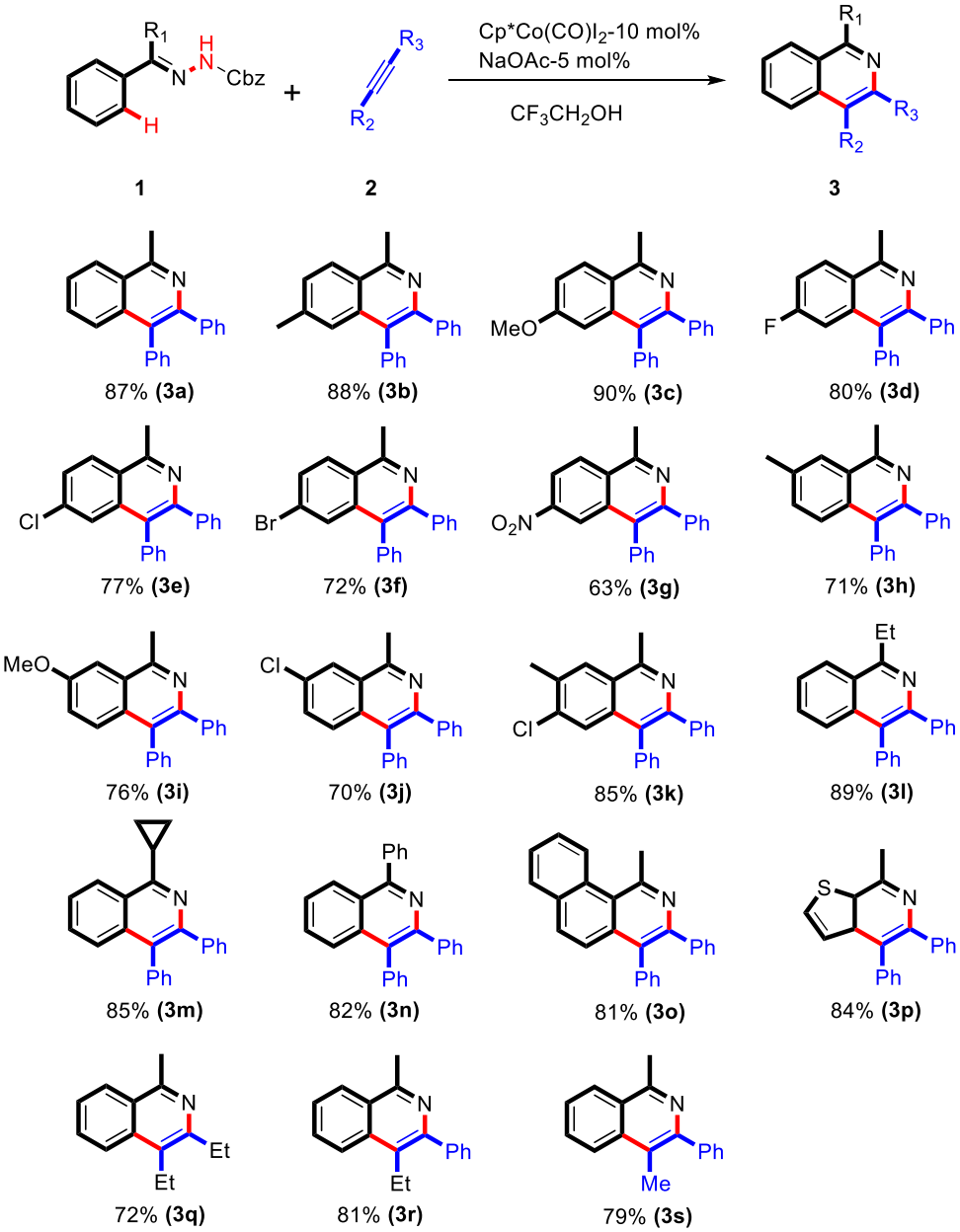
Our research expedites ortho C-H bond activation, utilizing Cp*Co(III) in a redox-neutral cyclization with the seldom-studied N-Cbz hydrazone, providing an elegant, cost-effective, and user-friendly method for isoquinoline synthesis without the need for silver salt and with an external oxidant.

Results and discussion

Optimizing reaction conditions using 0.5 mmol N-Cbz hydrazone and diphenylacetylene in 2 mL trifluoroethanol with Cp*Co(CO)I2, NaOAc, and AgSbF6 resulted

in a satisfactory 71% yield for isoquinoline 3a at 100 °C for 16 hours; further screening revealed varying impacts of acetate sources and solvents on product yield, with the absence of silver hexafluoroantimonate salt surprisingly having no effect on the final yield.

Raising the reaction temperature to 110°C significantly impacted product yield, while no change was observed at 120°C. Extending reaction time to 18 hours had no effect, but reducing it to 14 hours resulted in a lower yield. The optimal catalyst loading for the model reaction was found to be 10 mol% (Table 1, entries 12–17).



Scheme 2. The scope of substituted *N*-Cbz hydrazones and Alkynes.[a]

Under optimized conditions, our versatile protocol produced promising isoquinoline products (87–78% yield) from various substituted N-Cbz hydrazones, showcasing adaptability with electron-donating and -withdrawing groups. Notably, substituting N-Cbz hydrazone without a substitute yielded product 3a significantly, and introducing methyl and methoxy groups increased yields (88% and 90% for 3b & 3c). Electron-deficient groups (fluoro, chloro, bromo, nitro) yielded products with 80%, 77%, 72%, and 63% yields (3d-3g), and varied

positions of functional groups minimally impacted yields. The reaction with diphenyl acetylene and meta-methyl N-Cbz hydrazone resulted in a 71% yield (3h). Annulating disubstituted N-Cbz hydrazones yielded product 3k with an 85% yield. Isoquinoline products from various ketones (3l, 3m, 3n, 3o) showed yields of 89%, 85%, 82%, and 81%, respectively.

Diphenyl acetylene and N-Cbz hydrazone, derived from a heterocyclic ketone, effectively yield the desired product (3p) in satisfactory yield. Exploring various N-Cbz hydrazones, we further investigated different alkynes for isoquinoline derivative preparation, where 3-hexyne and unsymmetrical alkynes (but-1-yn-1-ylbenzene and prop-1-yn-1-ylbenzene) produced the corresponding products (3q, 3r, 3s) with good yields.

Conclusion

Developed a redox-neutral Cp*CoIII-catalyzed dehydrative cyclization of N-Cbz hydrazones with alkynes, eliminating the need for silver salt or an external oxidant, yielding multi-substituted isoquinoline derivatives efficiently.

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13

Design, synthesis, spectral characterization and anti-microbial screening of some novel 1, 2, 4- dithiazole with Coumarin moiety.

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ABSTRACT

One step synthesis of 7-(3-substitutedimino-1,2,4-dithiazolo)-4-methyl-2H-chromen-2-one (IIa-e) was carried out by oxidative cyclisation of 7-(5-substituted-2,4-dithiobiureto)-4-methyl-2H-chromen-2-one (Ia-e) by using liquid bromine in chloroform medium as an oxidizing agent. The synthesized compounds from these reaction conditions were characterized on the basis of elemental analysis, chemical characteristic and IR, PMR MASS, spectral data and antimicrobial activity against gram positive and gram-negative bacteria such as S. *typhi*, E. *coli*, S. *aureus*, A. *aerogenes*, B. *subtilis* and B. *megatherium.* etc.

Keywords: 7-(5-substituted-2,4-dithiobiureto)-4-methyl-2H-chromen-2-one, liquid bromine, chloroform, ammonium hydroxide ethanol, gram positive and gram-negative bacteria etc.

INTRODUCTION

Organic compounds containing thiadiazol[1] as the heterocycles in their structure are identified for their biological activities, pharmaceutical activities, industrial applications, agricultural purposes and in medicinal sciences[2-3]. Basically, structure of thiadiazol is five member nitrogen and sulphur containing heterocyclic compound. Presence of sulphur and nitrogen in its structure enhances the biological potential of the thiadiazol. Kalogirou[4] had reported 1,2,3-dithiazole for the antimicrobial activities, Laitinen *et al.*[5] reported the 1,2,3-dithiazole for the antibacterial activities, Matysiak[6] had reported thiadiazol and some different substituents attached thiadiazol directly or indirectly shows effect directly in their biological, medicinal property.

Similarly, Sayed[7] has prepared the thiadiazol based coumarin the best antimicrobial activities. The biological as well as industrial applications of coumarin[8] get enhanced due the presence of the thiadiazol nucleus in their structure. This 1,2,4-dithiazole synthesis technique is quicker, less complicated, less expensive and requires less time.

MATERIAL AND METHOD

Material

All the chemical used were of loba chemie (AR grade).

Method:

In the present experiment for the synthesis of different substituted 7-(3-substitutedimino-1,2,4-dithiazolo)-4-methyl-2H-chromen-2-one by using liquid bromine in chloroform medium. Reaction mixture was kept at room conditions for 4 hours**.**

EXPERIMENTAL

All the chemicals used for the synthesis must be purified. After refluxing the purity of the compounds were checked by TLC (aluminium TLC) with thin layer thickness of 200 um. The melting points of all synthesize compounds will be recorded using hot paraffin bath. The carbon and hydrogen analysis were carried out on Carlo-Ebra-1106 analyser Nitrogen estimation were carried out with colmon-N-analyzer-29. IR spectra were recorded with Bruker

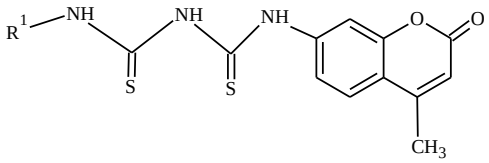
spectrometer in the range 4000-400 cm^{-1}. PMR spectra were recorded on VARIAN 400 MHz spectrometer with TMS as internal standard using $CDCL_3$ and DMSO Solvent.

GENARAL PROCEDURE

In a clean China dish paste of 7-(5-substituted-2,4-dithiobiureto)-4-methyl-2H-chromen-2-one **(Ia-e)** was prepared in chloroform and 5% liquid bromine in chloroform (2 ml) was added with constant stirring at room conditions. During the addition of bromine solution to firstly the colour of bromine disappear, addition of bromine was continued till colour of bromine appears and persists to the paste. Reaction mixture was kept for 4 hours at room conditions. On basification of the reaction mixture with dilute ammonium hydroxide solution, pale yellow solid of **(IIa-e)** obtained.

Similar procedure was adopted for the synthesis of all the derivatives in the series. The tentative reaction for the formation of product is depicted below,

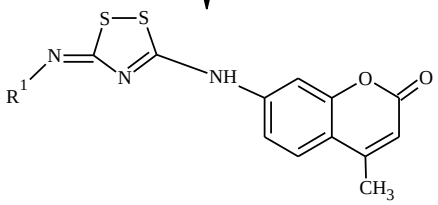
Reaction



7-(5-substituted-2,4-dithiobiureto)-4-methyl-2H-chromen-2-one

(Ia-e)

Br_2 $CHCl_3$



7-{[3-(substituted)-1,2,4-dithiazol-5-yl]amino}-4-methyl-2*H*-chromen-2-one

(IIa-e)

Similarly, 4-methyl-7-{[3-(phenylimino)-1,2,4-dithiazol-5-yl]amino}-2*H*-chromen-2-one **(IIb),** 7-{[3-(*tert*-butylimino)-1,2,4-dithiazol-5-yl]amino}-4-methyl-2*H*-chromen-2-one **(IIc),** 4-methyl-7-({3-[(4-methylphenyl)imino]-1,2,4-dithiazol-5-yl}amino)-2*H*-chromen-2-one **(IId)** and 7-({3-[(4-chlorophenyl)imino]-1,2,4-dithiazol-5-yl}amino)-4-methyl-2*H*-chromen-2-one **(IIe)** were synthesized from the oxidative cyclisation 7-(5-phenyl-2,4-dithiobiureto)-4-methyl-2*H*-chromen-2-one **(Ib)**, 7-(5-*tert*-butyl-2,4-dithiobiureto)-4-methyl-2*H*-chromen-2-one **(Ic)**, 7-[5-(4-methylphenyl)-2,4-dithiobiureto]-4-methyl-2*H*-chromen-2-one (**Id)** and 7-[5-(4-chlorophenyl)-2,4-dithiobiureto]-4-methyl-2*H*-chromen-2-one **(Ie)** with liquid bromine in chloroform medium respectively by the above mentioned procedure.

RESULT AND DISCUSSION

Spectral characterization results for all the synthesized compounds are given below

Spectral Characterization

1) **7-{[3-(Ethylimino)-1,2,4-dithiazol-5-yl]amino}-4-methyl-2*H*-chromen-2-one (IIa)**
   Yellow solid, $C_{14}H_{13}N_3O_2S_2$, Yield-87%, M.P.-142 ^{0}C. %Composition found **(calculated):** C-52.59(52.64), H-4.07(4.10), N-13.14(13.15), O-10.01(10.01) and S-20.03(20.07). **IR spectrum (cm^{-1}):** 3130.50 (Ar C-H stretching), 1140.12(C=S stretching), 3340.43 (NH stretching) and 1740.41 (C=O strech lactone). **PMR spectrum:** The spectrum of a compound was carried out in $CDCl_3$. This spectrum distinctly displayed the signals due to singlet 3 protons of -CH_3 gives singlet at δ 2.4 ppm

due to attachment with aromatic ring, 3 protons of -CH= of aromatic ring gives doublet at δ 7.7, 7.74 and 7.3 ppm, 1 proton of -CH= of conjugated lactone gives singlet at δ 5.84 ppm, 2 protons of $-CH_2$ gives quartet at δ 3.5 ppm, 3 protons of $-CH_3$ gives triplet at δ 1.38 ppm, 1 proton -NH attached between thionyl group and phenyl ring also desheilded due to thioamide position and gives signal at δ 3.9 ppm. **Mol. Wt.:** 319.40.

2) **4-Methyl-7-{[3-(phenylimino)-1,2,4-dithiazol-5-yl]amino}-2*H*-chromen-2-one (IIb)**
Yellow solid, $C_{18}H_{13}N_3O_2S_2$, Yield-85%, M.P.-134 ^{0}C. **%Composition found (calculated):** C-58.78(58.83), H-3.53(3.56), N-11.43(11.43), O-8.70(8.70) and S-17.41(17.45). **IR spectrum (cm^{-1}):** 3050.12 (Ar C-H stretching), 1090.06 (C=S stretching), 3400.12 (NH stretching), 1753.94 (C=O strech lactone) and 1580.29 (NH bending). **PMR spectrum:** The spectrum of a compound was carried out in $CDCl_3$. This spectrum distinctly displayed the signals due to singlet 3 protons of $-CH_3$ gives singlet at δ 2.4 ppm due to attachment with aromatic ring, 4 protons of -CH= of aromatic ring gives doublet at δ 7.7, 7.3, 7.4 and 7.6 ppm, 1 proton of -CH= of conjugated lactone gives singlet at δ 5.85 ppm, 1 proton -NH attached between thionyl group and phenyl ring also desheilded due to thioamide position and gives signal at δ 3.8 ppm. **Mol. Wt.:** 367.44.

3) **Synthesis of 7-{[-3-(*tert*-butylimino)-1,2,4-dithiazol-5-yl]amino}-4-methyl-2*H*-chromen-2-one(IIc)**
Yellow amorphous solid, $C_{16}H_{17}N_3S_2O_2$, yield 85%, M.P. 110 ^{0}C, **% Composition found (calculated**), C-55.33(55.33), H-4.94(4.93), N-12.09(12.09), O-9.20(9.20), S-18.45(18.45). **IR spectrum (cm^{-1}):** 3450.12 (N-H stretching), 3034.72 (C-H Ar Stretching), 1560.56 (N-H Bending), 1120.12 (C=S stretching) and 1740.40 C=O stretching(lactone). **PMR spectrum**: The spectrum of a compound was carried out in $CDCl_3$. This spectrum distinctly displayed the signals due to singlet of 3H of $–(CH_3)$ at δ 2.42 ppm, singlet of 9H of $–(CH_3)_3$ at δ 1.35 ppm, singlet of 1H of -CH= of conjugated lactone gives singlet at δ 5.8 ppm, 3 protons of -CH= of aromatic benzene ring gives doublet at δ 7.7, 7.4 and 7.7 ppm and singlet of -NH at δ 3.4 ppm. **Mol. Wt.:** 347.45.

4) **4-Methyl-7-({3-[(4-methylphenyl)imino]-1,2,4-dithiazol-5-yl}amino)-2*H*-chromen-2-one (IId)**
Yellow solid, $C_{19}H_{15}N_3O_2S_2$, Yield-88%, M.P.-118 ^{0}C. **%Composition found (calculated):** C-59.76(59.82), H-3.93(3.96), N-11.01(11.01), O-8.38(8.38) and S-19.77(16.81). **IR spectrum (cm^{-1}):** 3052.15 (Ar C-H stretching), 1050.20 (C=S stretching), 3470.12 (NH stretching), 1735.12 (C=O stretch lactone), 1570.12 (NH bending) and 2930.52 C-H (CH_3 stretching). **PMR spectrum:** The spectrum of a compound was carried out in $CDCl_3$. This spectrum distinctly displayed the signals due to singlet 3 protons of $-CH_3$ gives singlet at δ 2.4 and 2.02 ppm due to attachment with aromatic ring, 5 protons of -CH= of aromatic ring gives doublet at δ 7.2, 7.7, 7.03, 7.3 and 7.6 ppm, 1 proton of -CH= of conjugated lactone gives singlet at δ 5.8 ppm, 1 proton -NH attached between thionyl group and phenyl ring also desheilded due to thioamide position and gives signal at δ 3.5 ppm. **Mol. Wt.:** 381.47.

5) **7-({3-[(4-Chlorophenyl)imino]-1,2,4-dithiazol-5-yl}amino)-4-methyl-2*H*-chromen-2-one (IIe)**
Yellow solid, $C_{18}H_{12}N_3O_2S_2Cl$, Yield-84%, M.P.-130 ^{0}C. **%Composition found (calculated):** C-53.74(553.79), H-2.98(3.009), N-10.45 (10.45), O-7.96(7.95) and S-15.92(15.95). **IR spectrum (cm^{-1}):** 3080.45 (Ar C-H stretching), 1160.50 (C=S stretching), 3470.15 (NH stretching), 1745.12 (C=O strech lactone), 1570.01 (NH bending) and 2950.63 C-H (CH_3 stretching). **PMR spectrum:** The spectrum of a compound was carried out in $CDCl_3$. This spectrum distinctly displayed the signals due to singlet 3 protons of $-CH_3$ gives singlet at δ 2.3 ppm due to attachment with aromatic ring, 4 protons of -CH= of aromatic ring gives doublet at δ 7.29, 7.78, 7.54, 7.35 and 7.60 ppm, 1 proton of -CH= of conjugated lactone gives singlet at δ 5.86 ppm, 1 proton -NH attached between thionyl group and phenyl ring also desheilded due to thioamide position and gives signal at δ 3.5 ppm. **Mol. Wt.:** 401.88.

CONCLUSION

In the present research work is cheaper and less time consuming method for synthesis of organic compound **(IIa-e**). In all the synthesized compounds give the maximum yield of product **(II a-e)**. A variety of coumarin based 1,2,4-dithiazole derivative can be synthesised for their antimicrobial activities adopting the method.

PHARMACOLOGICAL STUDIES

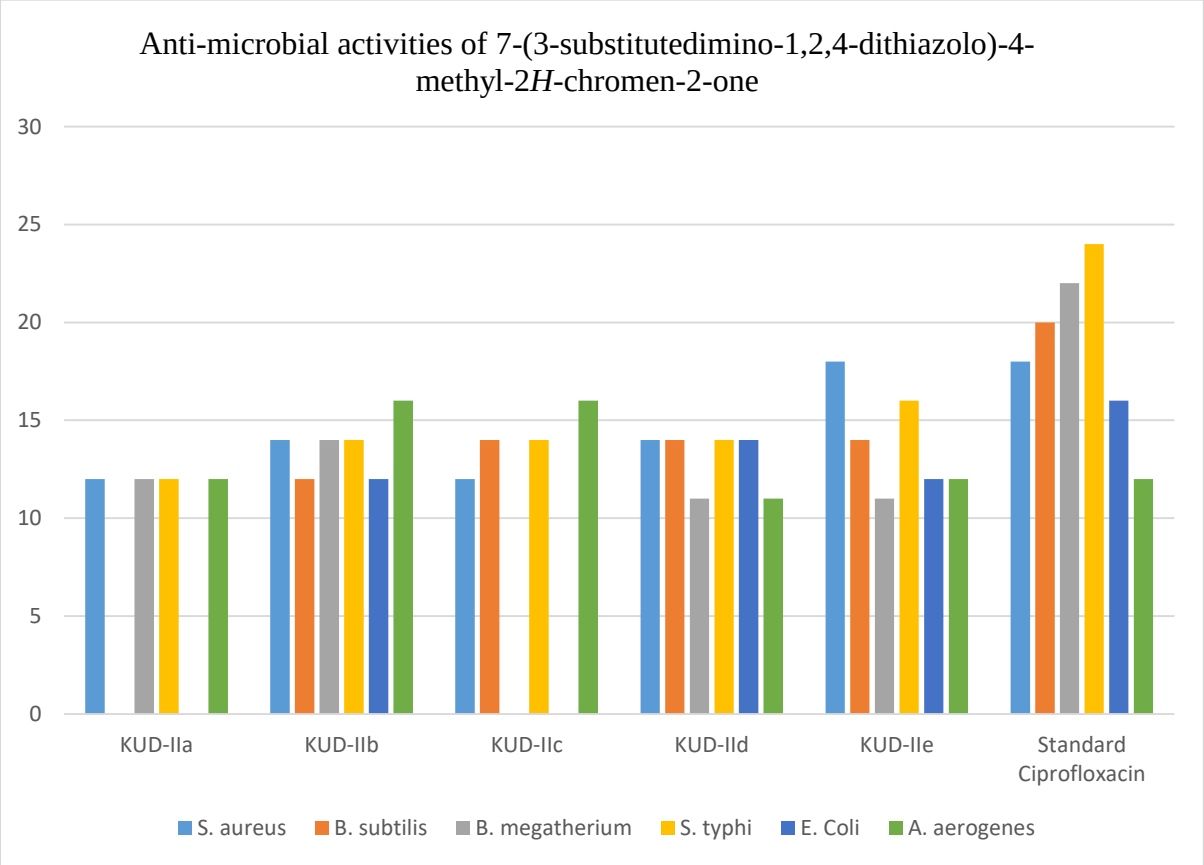
Antimicrobial Activity

All the synthesized compounds **(II-a)** to **(II-e)** were screened for antibacterial activity against S. *typhi*, E. *coli*, S. *aureus*, A. *aerogenes*, B. *subtilis* and B. megatherium. by disc diffusion method was performed using Mueller Hinton agar as well as nutrient agar medium. Each and every compound was tested at conc. 50 µg/ml in ethanol. The zone of inhibition of all the synthesized compounds were measured after 24-hour incubation at 37 ^{0}C. Standard drug used for comparison the activity was Ciprofloxacin.

Table 1: Synthesized compound **IIa-e** activity against Gram +ve and Gram -ve bacteria.

Table No. 1.1– Antimicrobial sensitivity test against bacteria (after 24 hours at 37 ^{0}C temp.)
(zone of inhibition in mm)

SR No.	Compd.	Gram positive			Gram negative		
		S. aureus	***B. subtilis***	***B. megatherium***	***S. typhi***	***E. Coli***	***A. aerogenes***
11	**KUD-IIa**	12	00	12	12	00	12
12	**KUD-IIb**	14	12	14	14	12	16
13	**KUD-IIc**	12	14	00	14	00	16
14	**KUD-IId**	14	14	11	14	14	11
15	**KUD-IIe**	18	14	11	16	12	12
27	**Standard Ciprofloxacin**	18	20	22	24	16	12



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14

Effect Of metal-ligand complexon germination of some vegetable plants

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Plant physiology will probably also assume an increasingly important role in agricultural research problems. As world population increases, mankind faces enormously complex problems. One of the primary tasks of the future will be to increase food, forage, fiber and wood production substantially throughout the world. Today the application of various chemical salts to soils is a basic feature of agricultural practice.

In the present work, Chalcone(an α,β-dihydroxy Ketone)treatment on Vegetable plant' is selected for study as they have both nutritional as well as medicinal value. Since organic drugs have intense biological activity and since no work is reported on the biological applications of binary complexes of Fe (III) with ligand(chalcone) and comparing with pure ligand, metal and control solution doubly distilled water to study the effect of complex, metal, ligand and control solution on germination survival, seedling height, etc. on fenugreek and Spinish plants in order to make suggestion whether complex, metal and ligands can be used as plant growth regulators.

The following aspects were studied in laboratory.

1) Estimation of Root / Shoot Ratio in soil & soilless media.

2) Estimation of chlorophyll contents in soil & soilless media.

EXPERIMENTAL:-

The information about the role of metal complexes in biological systems, their concentration and presence in different equilibria is of immense importance. Greshon et. al.[1, 2] reported that the activity of metal chelates is considerably increased as compared to that of the free metal and ligand alone on their complexation. The Shel et. al.[3] and Shashindharam et. al.[4] observed the antifungal and antibacterial activities of complexes shows that they are more active as compared to free ligand and metal involved.

Rare earth ions are used as probe in bio-chemistry of calcium. Zielinski et. al.[5] showed that, Lanthanide ion could substitute the calcium ion to produce active enzyme system. Some bivalent metal ions have been reported to be useful in agriculture as plant growth regulators. Such a vast uses of lanthanide necessitate concentrating on the study of lanthanides and ligands for studying the germination pattern.

The complexes of transition metal with bis-alkyl thiourea are prepared and their herbicidal and plant growth regulating activity are tested with wheat and cucumbers by Darnall et. al.[6].

Sayed amir et.al.[7] studied effect of some heavy metals on seed germination of canola, wheat, safflower evaluate phytoremedial potential.

K. Abraham et. al.[8] also studied effect of heavy metals on seed germination of archis hypogeae. L

Shivakumar C. K. et. al.[9] also observed the presence of beneficial fungus and effect of copper and zinc metal absorption on growth and metal uptake of legumineous plants as although these metals are required in traces but are important for growth.

A. Ramteke et. al.[10] studied the effect of chlorosubstituted pyrrazole and their complexes

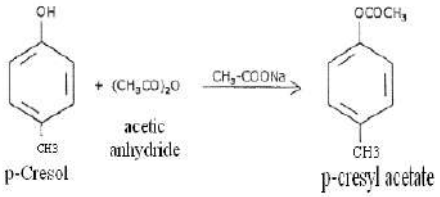
on spinach at different pH.

Recently J.G.Wu et. al[11] 18, 23 studied effect of complex on plants.

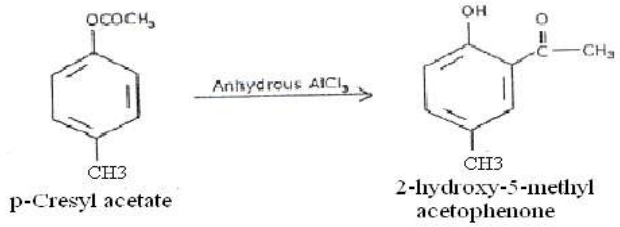
SYNTHESIS OF CHALCONE BY KNOWN METHOD

THE CHALCONE WAS PREPARED BY KNOWN LITERATURE METHOD AND WAS CONFIRMED BY MELTING POINT AND ALSO THE STRUCTURE WAS CONFIRMED BY IR SPECTROSCOPY AS SHOWN IN SPECTRA.

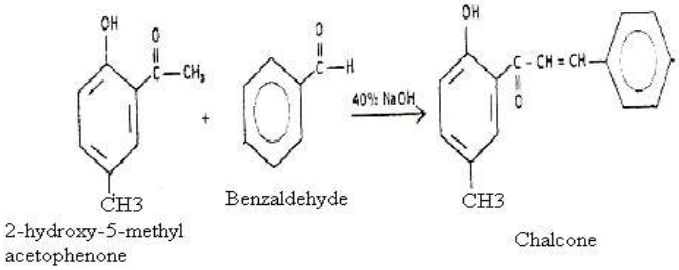
Step I: Preparation of p-cresyl acetate from p-cresol



Step II:Preparation of 2-hydroxy-5–methylacetophenone from p-cresyl acetate



Step III:Preparation of chalcone from 2-hydroxy-5-methyl acetophenone



MATERIAL AND EXPERIMENTAL METHODS

- ***Metal ions:-***

The solutions of metal ion in the form of $FeCl_3$ and MgCl2 of 0.1 M concentration were prepared using distilled water and the seeds of fenugreek and Spinach were soaked in both metal solvents.

- ***Ligand:-***

The organic compound was prepared were dissolved in proper solvent and above seeds are soaked for 2-3 hours.

Metal ion + Ligand:- The mixture of $FeCl_3$ and organic compound (chalcone) and MgCl2 and organic compound (chalcone) were dissolved in the distilled water and seeds are soaked.

Media:-For the germination of the above vegetables seeds, two types of the medias are used.

1) Soil media (media A)
2) Soilless media (media B)

EXPERIMENTS PERFORMED :-

In general practice, various chemicals are used in agricultural as an important ingredient of various pesticides, insecticides, fertilizers, etc. to improve the crop yield. Amongst several economical important plants Fenugreek and Spinach are selected as a plants system. These plants are in ideal systems to study the germination and growth pattern. Further, their economical importance is reflected by its wide use for food. The important uses these plants in daily life are persuasive to study its response against metal ion, ligand and its complex regarding to physiological processes; particularly germination is a vital process for the growth of plants. Therefore, these plants are selected as a plant system.

1]Healthy seeds were taken and thoroughly washed using doubly distilled water. Seeds from these healthy seeds of equal size were chosen, immersed in tested solution. These seeds soaked were taken out of each solution the seeds are sown in germination trays of all medias.

2]Effect of ligand, metal Fe (III), complex and metal Mg (II), complex on chlorophyll in the leaves of vegetables plants were studied.

After sufficient growth, green fresh leaves were collected, as they contain chlorophyll pigments and chlorophyll content was determined spectrophotometrically given by Jahagirdar D. V.[12]

ESTIMATION OF CHLOROPHYLL IN LEAF PIGMENT:-

Procedure:- Collect the fresh leaves weigh around 1 gm of leaves and cut them into small pieces. Add 5 ml of water and transfer the mixture to a blender. Homogenize the mixture by blending it intermittently for 3-4 minutes.Take 0.5 ml of homogenous mixture and add 4.5 ml of 80% acetone to it. Thoroughly shake the content, centrifuge it. Collect the supernatant liquid and measure its optical density at 645 and 663 nm.

- ***Parameters:-***Plants growth is decided on the basis of parameters such as percentage of germination survival, seedling height, shoot length, root length (root length / shoot length) and thickness of young leaf having high values compared to control system. The germination was noted after7days ,14 days and 22days for all Plants. After noteing the survival of the plants, they were taken out of the medias. The seedling height (root length / shoot length) was measured. The average values of these parameters are presented in Table 1

RESULT AND DISCUSSION

Some attempts have been made by Bera et. al.[13] to study the effect of tannery effluent on seed germination, seedling growth and chloroplast pigment content in mungbean. Adhikari et. al.[14] have observed the effect of raw savage water on mustard. Recently Farzin

M. Parabia et. al.[15] in their present investigation, effect of ligand, complex and metal ion on percentage seed germination, root length, shoot length (root / shoot ratio) has been studied.

ROOT LENGTH, SHOOT LENGTH AND ROOT / SHOOT RATIO

Germination starts when the seed shows emergence phase of growth, which begins, with penetration of embryo from the seed coat and end with development of root and shoot system. The elongation of shoot axis follows emergence of radical.

The rate and extent of elongation is subjected to a variety of controls, including nutrition, hormones and environmental factors. Though the root and shoot evelopment start within a fraction of time but the further developments may vary according to the nutrients required for the development of root and shoot independently. Therefore, root and shoot length differs from each other.

Table 1:-Effect of Different Treatment on Vegetable Plant in Respect of Parameters in Soil and Soilless Media.

Sr.No.	Parameters	Fenugreek		Spinach	
		Soil	Soilless	Soil	Soilless
1	% Germination	736%	86%	88%	90.4%
2	Seedling Height(cm)	11.96	12.26	9.77	10.6
3	Shoot Length(cm)	6.44	6.46	6.04	6.29
4	Root length(cm)	5.52	5.76	3.74	4.28
5	Shoot/Root Ratio	1.17	1.15	1.68	1.50

Table 1 clearly indicates that percent germination in soilless medium is higher followed soil media. Similarly the root length and shoot length which is called as seedling height shows a significant development of root / shoot length i.e. height of seedling highest in chalcone + Mg as compaired to over all the treatments and subsequently followed by chalcone + Fe, metal ion Mg, chalcone and control (d/w) respectively in all cases. When we compare the performance of all the treatments for different parameters in soil and soilless media. The germination & growth parameters are studied in soil and soilless media. Soilless media shows better performance as against soil media in all the treatments.

Mg is a major constituent for the formation of chlorophyll molecule which helps in the process of photosynthesis for the production of food materials in the plant i.e. sugar synthesis.With combination of chalcone + Mg plays a pinnacle role in keeping all the system working properly. This may be the reason for the better performance.

Fe plays major role in energy transfer within the plants and also brings about chlorophyll development and formation. It is also a constituent of certain enzyme and protein. With the combination of chalcone plays a major role in keeping all the plant system working properly may be the reason for a good performance.

The germination of seed and development of the seedling is better in soilless media than the soil media. Because there is less resistance for the root development and shoot

development in soilless media than the soil media may be the reason for better, overall development of the plant.

- ***CHLOROPHYLL CONTENT***

Photosynthesis is the process in which the light energy will be converted into chemical energy. There are some basic requirements for the process of photosynthesis as CO_2, H_2O and light energy besides of course, the structural framework of green plant in the form of chloroplast, which is a unique cell having most important role in all the physiological reactions, starting from the absorption of light energy. Basically, among the smallest group of coordinating pigment molecules necessary to effect a photochemical act, the most important pigments involved in photosynthesis are chlorophyll and carotenoid.

Table 2-3 clearly shows that absorption of plant leaves is higher at 663 nm in all the treatments. These tables also clearly indicates that the amount of chlorophyll is more in chalcone + Mg. Followed by chalcone + Fe, metal ion Mg, chalcone and control (d/w) in both soil and soilless media.

Obviously the chlorophyll content is highest in chalcone + Mg in both soil and soilless medias. Because of Mg is major constituent for the formation of chlorophyll.

Table 1:-Effect of different treatment on chlorophyll content in respect to soil media

Sr.No.	Nameof vegetable plants	Treatment with Ligand	Treatment with Ligand+Mg	Treatment with Ligand+Fe	Treatment with Metal ion Mg	Treatment with distilled water
1	Fenugreek	$8.22x10^{-3}$	$10.162x10^{-3}$	$8.363x10^{-3}$	$11x10^{-3}$	$5.64x10^{-3}$
3	Spinach	$4.71x10^{-3}$	$7.65x10^{-3}$	$5.61x10^{-3}$	$8.09x10^{-3}$	$4.50x10^{-3}$

Table 2:-Effect of different treatment on chlorophyll content in respect to soilless media

Sr.No.	Nameof vegetable plants	Treatment with Ligand	Treatment with Ligand+Mg	Treatment with Ligand+Fe	Treatment with Metal ion Mg	Treatment with distilled water
1	Fenugreek	$11.9x10^{-3}$	$14.8x10^{-3}$	$12.5x10^{-3}$	$19.3x10^{-3}$	$10.3x10^{-3}$
3	Spinach	$7.41x10^{-3}$	$8.45x10^{-3}$	$8.31x10^{-3}$	$9.93x10^{-3}$	$5.41x10^{-3}$

When we compare the performance of all treatments for different parameters, in soil and soilless medias. It is clearly observed that soil less media shows better result in respect of germination percentage, development of seedling during the experimental period.

Result of effect of metal ion Mg, Chalcone, Chalcone+ Mg and control (d/W) and chalcone+ fe, on germination, seedling development clearly revels that, Chalcone +Mg shows significant better performance overall the treatments. All the parameters are considered, while finding out the results. In general order in all the parameters performance wise Chalcone+Mg stood first followed by metal ion Mg, Chalcone Chalcone+fe and control (D/W).

The germination and growth parameter are studied in soil and soilless media. The soilless media shows better performance as against the soil media in all the treatments.

Mg is major constituents for the formation of chlorophyll molecule which helps in the process of photosynthesis for the production of food materials in the plants ,i.e sugar synthesis with the combination of Mg chalcone plays a pinnacle role in keeping all the plant system working properly may be the reason for a better performance.

Mg is a secondary importance element essential for the plant growth. Which is also a constituents of many enzyme the detail information about Mg is already mention in the above para. So, keeping in view of all the characteristics of Mg plays a pivotal role for a good performance against the other treatments.

Germination of seed and development of seedling is better in the soilless media than the soil media, because there is less resistance for the root development and shoot development on the soilless media than the soil media, may be the reason for better overall development of the plant.

The analysis perform for finding out the total chlorophyll in green leaves of the plant. The results of analysis clearly indicates that metal ion Mg is having highest chlorophyll content in both soil and soilless media than the remaining treatment like Chalcone+Mg, Chalcone+fe , Chalcone and control (D/W).

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15

Preparation of Adsorbent from various natural materials for removal of heavy metal ions from waste water: Critical review.

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Abstract

Anthropogenic and industrial activities release heavy metal ions into the water. They may be poisonous or carcinogenic in nature and has serious risks to both aquatic environments and people. Heavy metal removal from wastewater is a severe issue as a result. The adsorption method is advantageous for removing heavy metals from wastewater due to its accessibility, affordability and eco-friendliness. High removal capacity of commercial adsorbents and bio adsorbents are both utilized to remove heavy metals from wastewater. This review article intends to gather erratically collect data on the many adsorbents used for heavy metal removal and to provide details on the commercially available and natural bio adsorbents utilized in particular for the removal of copper, lead, Nickel and cadmium.

KEYWORDS: Biosorption, Bio adsorbent, Heavy Metals ions.

1. Introduction

Environmental contamination is one of the major issues of this century as a result of industrial development and the manufacturing of diverse industrial products around the world. [1] Heavy metal mercury can accumulate more quickly in cropland and bodies of water as a result of mining, smelting and sewage irrigation. Through sewage irrigation, mercury can go to crops, which could be harmful to human health. [2]A significant amount of chromium is found in the waste water from chromium mining, smelting, manufacturing, planting, metal processing, tanning, paints and pigments, printing and dyeing. Recently there has been a lot of interest in studying how to use agricultural waste products as adsorbents to remove heavy metals from industrial effluents. A component of biotechnology is the use of agricultural by-products in the process known as bio-sorption to remove heavy metal ions from the environment. This is acknowledged as a new method for treating heavy metal-polluted streams. The metals of immediate concern, according to the World Health Organization are Cr (III), Cr (VI), Zn, Cd, Cu, Ni, Hg, Pb, Al and Mn. [4]Environmental pollution brought on by human activity has grown dramatically over the past few decades and has reached alarming levels in terms of its negative effects on living things. [5] The higher concentration of heavy metals causes adverse changes in color, test, odor of water and it also stains clothes and utensils. The Overload of heavy metals may cause severe health problems such as liver cancer, diabetes, cirrhosis of liver, disease related to heart and central nervous systems, infertility, etc. [10]

2.Material and Methods: -

Sr no.	Name of adsorbent used	Heavy metal ion removal	Initial conc. ppm or mgl-	pH	Contact time in minuts/hr.	Adsorbent amount	Maximum adsorption capacity	Langmuir isotherm fit	Reference
1	Soybean oil residue	Cd, Zn, Pb	100-300	1-5	1-60 Cd=40min Zn=20min Pb=10min.	0.02-2gm			T.Mahamudiono(2022)
2	1.Biochar(B) 2.Modified biochar (MB) 3.Bentonite (BE) 4.Biochar – bentonite composite	Hg^{2+}	0.5-20		2hr		11.722 ,9.152		Y.Bai and J. Hong (2021)
3	Wheat straw, Corn straw	Cr(VI) Cr(III)	200	3 5			125.6 68.9 87.4 62.3	Langmuir	Y.Chen (2020)
4	1.Carbonized corn husk 2.Uncarbonised corn husk 3.carbonised Millet husk 4. uncarbonized Millet husk 5.carbonized husk 6.Uncarbonzed husk	Cr Ni Mn	1.5	2-10	20min-40min	0.2-0.6 Agitation rate(100-300 rpm			S.M. Batagarawa (2019)
5	Wheat Bajra Sugarcane corn	Cu	5.55	5 5.6 5.8 5.6			98%		N.N. Bandela (2016)

6	Carbonized milet husk, Acid treated corbonised millet husk	Pb(II) Cd(II)Ni (II)			40min 100rpm	50mg 100rpm	98% 94% 94% 97% 92% 94%	FTIR SEM	S.M .Batagarawa (2017)
7.	Modified Nanokaoline (NK), Modified Nanobentonite (NB)	Zn^{2+}	4	6	70	400	167mgg-1 143mgg-1	Langmuir Freundlich, Temkin Dubnin Raushkevich SEM	B.U. Maheswari (2019)

3.Discussion

The synthetic and industrial waste water samples were treated by using different natural materials to remove different types of heavy metal ions. These natural materials are adsorbents are simple to produce and their raw materials are widely accessible. Hence, it is a green technology that significantly improves the wastewater treatment process. In general, the most practicable approaches are chemical, adsorption, and membrane techniques. There should be more study done on the introduction of low-cost materials and techniques for heavy metal removal from wastewater. Future study should consider the best methods for achieving effective metal recovery with minimal negative effects on the environment and low costs.

4.Conclusion

One such method that not only addresses the removal of heavy metals from wastewater but is also eco-friendly and has a small environmental impact is adsorption. Adsorbents like activated carbon are commonly employed, although their use is limited by their expensive price. As a result, it's important to consider sustainable solutions that also address the problem's wider implications. Agricultural wastes, industrial wastes, and biochar are inexpensive, easily accessible, renewable, and have a strong affinity for heavy metals, the use of these low-cost bio sorbents is used. As a result, the availability of agro-wastes as a cheap method for removing harmful heavy metals from waste water [(5).] The adsorbents are simple to produce and their raw materials are widely accessible. Hence, it is a green technology that significantly improves the wastewater treatment process.

5. Acknowledgement

Further work on creating more affordable adsorbents may aid in the remediation of heavy metals.

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16

Evaluation of Antioxidant Activity by DPPH Method of Thiocarbamides

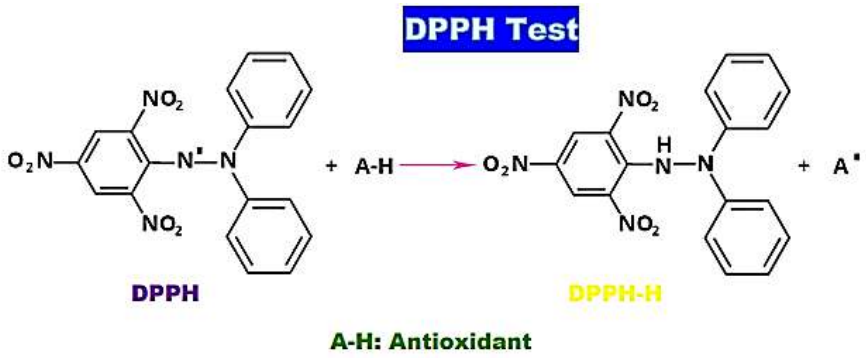
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ABSTRACT

The DPPH free radical scavenging method is recognized and reliable for the evaluation of the antioxidant activity of chemical compounds. The antioxidant capability of thiocarbamate compounds was characterized by its color change with DPPH (2,2-Diphenyl-2-Picrylhydrazyl) and further analyzed its percentage scavenging activity with strong absorption at 517 nm. Utmost thiocarbamate compounds had incomparable percentage scavenging activity and displayed lower IC50 values (effective concentration for scavenging 50% of the initial DPPH value (for µM) resolved excellent antioxidant activity as compared to ascorbic acid.

Keywords: Thiocarbamides, Antioxidant activity, DPPH method, IC_{50} value

Graphical Abstract:



1. Introduction:

Thiocarbamide compounds have wide spectrum applications in various fields such as pharmaceutical, agriculture, medicinal, and synthetic chemistry [1-5]. An antioxidant prevents the oxidation of molecules inside a cell. Free radicals produced during the biological oxidation chain reaction can lead to damage to a cell. Antioxidants act as reducing agents by terminating a biological chain reaction and eliminating free radical mediates, also preventing oxidative damage and protecting cells from severe body complaints [6-9]. Researchers are constantly working on synthesizing compounds with highly potent antioxidant activity [10-15]. The DPPH test is one of the very stable and reliable free radical scavenging methods to measure the antioxidant activity of organic compounds [16-21]. DPPH is reduced by accepting hydrogen from hydrogen donor compounds and free radical scavenging compounds reduction shows a colour change from violet to yellow. A study of antioxidant activity synthesized compounds was done by calculating its % scavenging activity values and half-maximal inhibitory concentration

values or effective concentration for scavenging 50% of the initial DPPH value (IC_{50} value) [22-24].

In the present study, the antioxidant activity of novel substituted thiocarbamide compounds was investigated by using the DPPH free radical scavenging method and comparing its activity with ascorbic acid.

2. Experimental Section:

2.1. General

All synthesized substituted thiocarbamide compounds were purified by recrystallization with ethanol. DPPH (2,2-Diphenyl-2-Picrylhydrazyl) and ascorbic acid of AR grade were used. Micropipettes are used for the preparation of the microliter solution. Absorption at 517nm was measured using a Systronic (2202 model) make Double-beam UV Spectrophotometer.

2.2. Antioxidant activity / DPPH free radical scavenging activity

Novel thiocarbamide compounds displayed antioxidant activity and were determined by using free radical scavenging against 2,2-Diphenyl-2-Picrylhydrazyl (DPPH). 0.2 µM DPPH solution was prepared in 95 % ethanol and used as the negative control. Then, different substituted novel thiocarbamide compounds 200 µg/ mL were mixed with DPPH solution which was then incubated in the dark for 30 min. at room temperature. Vitamin C is used as a standard for comparison because of its high inhibition ability with the presence of OH group stabilized free radical. The absorbance of the reaction mixtures was then measured at 517 nm. By using a spectrophotometer. Plotting the % scavenging against concentration gave the standard curve and the percentage scavenging was calculated from the following equation:

$$\% \text{ scavenging activity} = [(\text{Abs. Blank} - \text{Abs. Sample}) / \text{Abs. Blank}] \times 100.$$

Thiocarbamides have significant antioxidant activity show low IC50 value (half-maximal inhibitory concentration) by the DPPH method.

Table 1: Antioxidant activity expressed as IC50 values of TD5 thiocarbamides

Concentration (µg/ml) of TD5	% Scavenging Activity	IC50 value
50	45.03	1.44
100	56.12	6.57
150	65.48	11.70
200	74.44	16.84
250	85.58	21.97
300	93.73	27.11

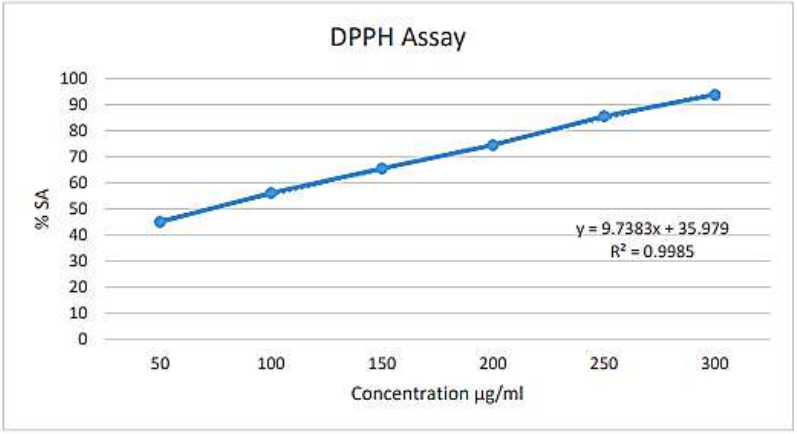
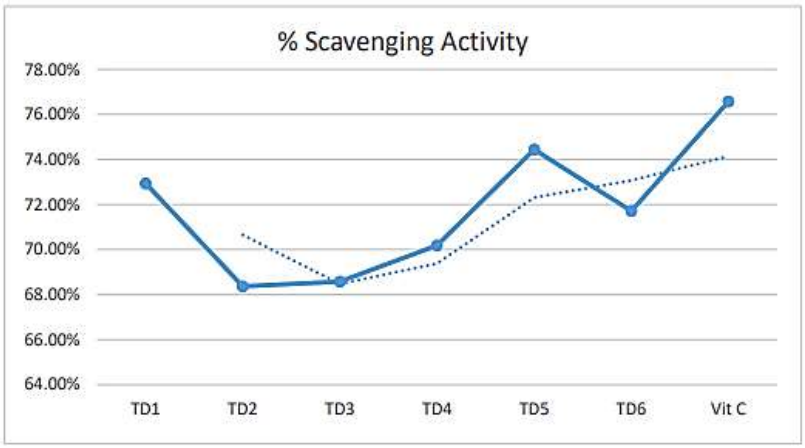


Table 2: Antioxidant activity of different thiocarbamides TD1-TD6

Thiocarbamide Derivatives 200 (µM) solution	**Ph-R**	**Abs.**	**% Scavenging Activity at 200 (µM)**
TD1	-H	0.254	72.94
TD2	-Me	0.297	68.37
TD3	-Allyl	0.295	68.58
TD4	-Ph	0.289	70.18
TD5	-PClPh	0.235	74.44
TD6	-mClPh	0.265	71.71
Vit.C		0.220	76.57



3. Result and Discussion:

Novel thiocarbamide compounds were investigated for their free radical scavenging ability in ethanol by using DPPH assay as DPPH radical changes from Purple to yellow color when quenched by antioxidants. DPPH radical scavenging was monitored by a Spectrophotometer at wavelength 517 nm. Most of the derivatives showed notable antioxidant properties as compared to Vitamin C. The Order of the activity depends on the free radical stability form in the derivatives.

In the present research work, all the thiocarbamide compounds showed excellent antioxidant activity with minimum IC50 values and at the lower concentration due to the presence of the N-H group in its structure.

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Declaration:
Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: This has not been published elsewhere and is not currently under consideration for publication elsewhere

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17

Investigations of Proximate Compositions of *Xanthium Strumarium L* Roots from Tisgaon (PIN Code 431002) of Taluka and District Aurangabad, India

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Abstract

Xanthium Strumarium L showed anti-oxidant, anti-inflammatory, anti-cancer activities as well as various medicinal significances hence it created sufficient interest to carry out proximate investigations of roots of *Xanthium Strumarium L* of Tisgaon (PIN Code 431002) of Taluka and District Sambhaji Nagar (Aurangabad), India which is hither to unknown from this region. Recently proximate investigations of roots of *Xanthium Strumarium L* of Tisgaon were successfully carried out and the present work deals with the quantitative analysis and identification of ash content moisture content as well water solubility, acid and base solubilities of *Xanthium Strumarium L*. which is important and essential part of herbal drugs in pharmacokinetics and pharmacodynamics of that particular drug. These factors directly hamper pharmacokinetics and pharmacodynamics of particular drugs and ultimately drug activity and drug effect of any synthetic, semi-synthetic and herbal drugs, hence it become essential to carry out proximate analysis of roots of *Xanthium Strumarium L* as they possess medicinal applications and significances. During this study it is investigated that, the roots of *Xanthium Strumarium L*. contain moisture and ash contents as well as acid-insoluble ash value, is determination of solubilities in cold water, hot water, and 1 percent NaOH, HCl, CH_3COOH are also investigated.

Keywords: *Xanthium Strumarium L*, roots, proximate investigations, quantitative analysis.

Introduction

In the tropical regions of India, *Xanthium Strumarium L.*, a member of the Composite family, is frequently seen growing along roadsides, in fields, and in hedges. The word "xanthium" refers to the seedpods, which change from green to yellow as they ripen (later they become deep yellow to brown), and is derived from the ancient Greek words "xanthos," which means "yellow," and "Strumarium," which means "cushion-like swelling." It is frequently referred to as "chota-gokhru" because of the fruit's resemblance to a cow's toe. It is used to treat the common condition hemicrania and is known as adhasisi in various parts of India. There are 25 species in the genus Xanthium, all of which are native to America. The medicinal plants *Xanthium Spinosum Linn.* and *X. Strumarium Linn.* are used in Europe and North America.

Sambhaji Nagar previously known as Aurangabad is one of the oldest and historical city in Maharashtra state of India encompass numbers of medicinal plants. Warmer climate is good for *X. Strumarium L*. It is an annual herb and grows up to 1 m tall and has a short, sturdy, hairy stem. The roots of *X. Strumarium L* contain tap root and secondary roots which are irregularly lobed. *Xanthium Strumarium L* is traditional herbal medicine which is used to treat bacterial, antifungal, urticaria and rheumatism infections as well as for the treatment of arthritis, rhinitis, nasal sinusitis, headache problems by vaidu and *X. Strumarium L*. showed reportable gastric ulcer, malaria, cancer, leprosy and leucoderma activies[1-8]. As a wider

program of this laboratory on natural products; various proximate investigations of different plants of various regions have been investigated in sufficient details[9-13], considering all these facts it was thought interesting to investigate proximate constituents present in roots of *Xanthium Strumarium L.* of Tisgaon (PIN Code 431002) of Taluka and District Aurangabad, India.

Materials and Methodology

All chemicals used during the research work were of A.R. grade. Freshly prepared solutions were used throughout the research work. The solvents were purified by known literature methods[14].

Sample Preparation: The plants were collected from farms of Tisgaon of Taluka and District Aurangabad, India in May 2023. The plants were cut along with the stem and shade dried. Dried roots were taken in mortar pestle and crushed to prepare fine powder. This fine powder is used for proximate investigations by known literature metods[15].

Proximate Analysis

The determination of physicochemical parameters such as moisture content, total ash value, acid-insoluble ash value, and solubility of the sample was carried out by the known literature methods[15]. Solubility of the sample was checked in cold water, hot water and 1 percent NaOH, HCl, CH_3COOH solution. Percentage of moisture and ash contents and acid insoluble ash are determined by using following formula,

$$\% \text{ of moisture} = \frac{\text{Loss of weight of sample}}{\text{Weight of sample taken}} \times 100$$

while,

Percentage of solubility is determined by using following formula,

% of Solubility=(loss of weight of sample)/(weight of sample taken) ×100

The results obtained are given in **Table-1**

Table-1

Sr. No	Proximate Parameters	Loss of weight of sample	Amount of sample taken (in grams)	%
1	Moisture content	0.220	1	22.00
2	Total ash content	0.165	1	16.50
3	Acid insoluble ash value	0.42	1	42.00
4	Coldwater solubility	0.67	1	67.00
5	Hot water solubility	0.48	1	48.00
6	NaOH solubility	0.46	1	46.00
7	HCl solubility	0.54	1	54.00
8	CH_3COOH solubility	0.137	1	13.70

Result and Discussion

Moisture content in any part of plant provides information for an activity of water-soluble enzymes and coenzymes needed for the metabolic activities of that plant and it is observed from Table No.-1 that, total moisture content in roots of was found to be 22.00% which is good for metabolic activities in the plant growth and development of the plant. It was found that the total ash content obtained from dry roots is 16.50% and acid insoluble ash value is 42.00% which are good and these proximate parameters of plant organs are useful for the determination of the mineral contents. Coldwater solubility and hot water solubility were found to be 67.00% and 48.00% respectively; these proximate parameters will gave information regarding water soluble neutral, acidic, basic and hydrocarbons present in the samples in herbal chemistry. HCl solubility and CH_3COOH solubility were found to be 54.00% and 13.70% respectively, these proximate parameters gave information regarding basic organic components present in the sample and

NaOH solubility was found to be 46.00% which gave information regarding acidic organic components present in the sample.

Conclusion

The Results obtained during proximate analysis were good and it can be conclude that, in roots of *Xanthium Strumarium L.* of Tisgaon (PIN Code 431002) of Taluka and District Aurangabad, India contain good proximate parameters and the physicochemicals well as physiological and anatomical activities of *Xanthium Strumarium L.* herbs at Tisgaon (PIN Code 431002) of Taluka and District Aurangabad, India are in natural form and can be used for medicinal purpose.

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18

Synthesis, Structural Study of Substituted Heterocyclic Compounds

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Abstract: Dithiazolidine constitutes a major role in the synthesis of various heterocyclic moieties. They act as active precursors in synthetic heterocyclic chemistry. Synthesis of a series of novel five member ring containing nitrogen and sulphur are well known[1].A series of novel 3-thio-4-substituted-5-tolyl-[1, 2, 4]-dithiazolidine [hydrochloride] have been synthesized by the interaction of several Ammonium aryl dithiocarbamate with *N*-*p*-tolyl-*S*-chloro isothiocarbamoyl chloride in refluxing chloroform medium. The newly synthesized compounds have been characterized by analytical and IR, ^{1}H NMR and Mass spectral studies.

A small heterocyclic ring containing nitrogen and sulphur have been under investigation for a long time because of their important properties. Synthesis, structural properties and antimicrobial activities of various [1, 2, 4]-dithiazolidine have been reported earlier[2]. The literature survey revealed that the [1,2,4]- dithiazolidine have been found to possess potent anti-tumors, anti-tuberculosis[3], anti-diabetic and anti-cancer[4] and anti inflammatory[5] properties.

Thiocarbamides and their heterocyclic derivatives have gained recently much interest as inhibitors of Human Immunodeficiency Virus (HIV)[6] and Therapeutic agents[7]. Some of the heterocyclic derivatives of thiocarbamides are found to possess diverse pharmacological activities like antifungal and anti-tubercular agents. In view of utility of thiocarbamides, N-aryl-S-chloro isothiocarbamoyl chloride have been used in synthesis of substituted [1, 2, 4] dithiazolidine by interacting with Ammonium aryl dithiocabamates. The drug containing 1, 2, 4-dithiazolidines show a diverse range of physiological activities, antimicrobial[8-9], anti-inflammatory[10-12], anti-ulcer[13-14], and anti-cancer[15]. Here is reported the synthesis of several 3-thio-4- substituted -5-tolyl-[1, 2, 4]-dithiazolidine [hydrochloride] (3a-g) have been synthesized by the interaction of several Ammonium aryl dithiocarbamate (1a-g) with *N*-*p*-tolyl-*S*-chloro isothiocarbamoyl chloride (2). The required Ammonium aryl dithiocarbamate (1a-g) were obtained by the interaction of interaction of different amines with carbon disulphide and Ammonia.

Results and discussion

Several 3-thio-4- substituted -5-tolyl-[1, 2, 4]-dithiazolidine [hydrochloride] (3a-g) have been synthesized by the interaction of several Ammonium aryl dithiocarbamate (1a-g) with *N*-*p*-tolyl-*S*-chloro isothiocarbamoyl chloride (2). in $CHCl_3$. After condensation, the solvent was distilled off to obtain a sticky residue. This residue was triturated several times with petroleum ether (60-80^{0}C) to afford a pale yellow solid (3a-g). The product was found to be non-desulphurrizable when boiled with alkaline lead acetate solution. The IR spectra of products shows bands due to Ar-H, C-H, C=N, C-C, C-N, C=S, C-S, S-S stretching and ^{1}HNMR spectra of products distinctly displayed signals due to aromatic protons and Acetyl protons. The Mass spectrum of product was also observed. The identities of these new 3-thio-

4-aryl-5-tolyl-[1, 2, 4]-dithiazolidine [hydrochloride] have been established on the basis of usual chemical transformations and also IR, ^{1}H NMR and Mass spectral studies[16-18].

Experimental

General Methods

All chemicals were research grade. Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI(4000-450cm^{-1}) spectrophotometer. ^{1}H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as internal reference. The Mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectrometer. Thin layer chromatography (TLC) was performed on silica Gel G and spots were visualized by iodine vapour. The compounds describe in this paper were first time synthesized by the multistep reaction protocol.

Synthesis of Ammonium aryl dithiocarbamate[19] (1a-g)

The compound Ammonium aryl dithiocarbamate was prepared by drop wise addition of Amine [9ml] in ice cold mixture of ammonium [15ml, density 0.88] and carbon disulphide [7.5ml] followed by the vigorous shaking. The reaction mixture was allowed to stand for 30min heavy precipitate of Ammonium aryl dithiocarbamate separates out. Filter it and dry it.

Synthesis of *N*-*p*-tolyl-*S*-chloro isothiocarbamoyl chloride (2)

The *N*-*p*-tolyl-*S*-chloro isothioocarbamoyl chloride was prepared by the interaction of p-tolyl isothiocyanate and by passing calculated quantity of Cl_2 gas. Details of typical experiment are as follows:

Through the chloroformic solution of *p*-tolyl isothiocyanate (0.002 M, 0.298 g in 15 mL) pure and dry chlorine gas (0.71g) was passed maintaining the temperature below 10^{o}C. Chlorine gas was generated by the addition of 35% HCl to $KMnO_4$. After the complete addition of chlorine gas, the resultant yellow solution was filtered to remove suspended impurities and the clear solution was mixed with petroleum ether (60-80^{o}C). The solvent was then removed by distillation under vacuum. The resultant oil was again diluted with petroleum ether and distilled under vacuum. *N*-*p*-tolyl-*S*-chloro isothiocarbamoyl chloride was obtained as pale yellow oil (1.00 g).

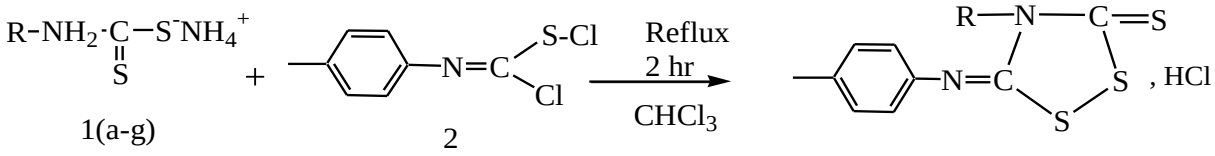
3a:- Synthesis of 3-thio-4-substituted-5-tolyl-[1, 2, 4]-dithiazolidine [hydrochloride]

A mixture of Ammonium phenyl dithiocarbamate (1a-g) and N-tolyl-*S*-chloro isothiocyanocarbamoyl chloride was gently refluxed for 2 hr during which evolution of HCl was noticed. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was brought to room temperature and the solvent removed under reduced pressure to obtain residue. This residue was triturated several times with petroleum ether (60-80^{o}C) to afford a pale yellow solid **(3a)**.

3a: IR (KBr) :υ 3155.5 (Ar-H), 2951.0 (C-H aliphatic), 1593.2 (C=N), 1508.3 (C-C), 1131.0 (C-N), 1143.7 (C=S), 752.2 (C-S), 503.4 (S-S), cm^{-1}; ^{1}H NMR (δ in ppm, $CDCl_3$): δ 7.94-7.22 (9H, m),; δ 2.358-2.353 (3H, s, CH_3) Mass (m/z): 316 (M^+), 300, 225, 211 , Anal. Calcd for $C_{15}H_{12}N_2S_3$, HCl: C, 56.96; H, 3.79; N, 8.86; S, 30.37; Found: C, 56.92; H, 3.75; N, 8.90; S, 30.34.

On the basis of all above facts the product with m. p. 122°C was assigned the structure 3-thio-4-phenyl-5-tolyl-[1, 2, 4]-dithiazolidine [hydrochloride]

When the reaction of *N*-*p*-tolyl-*S*-chloro-isothiocarbamoyl chloride was extended to several other Ammonium phenyl dithiocarbamate corresponding 3-thio-4-aryl-5-tolyl-[1, 2, 4]-dithiazolidine [hydrochloride] (3b-g**)** have been isolated.



Ammonium aryl dithiocarbamate

N-p-tolyl-S-chloro-isothiocarbamoyl chloride

3-thio-4-aryl-5-tolyl -[1, 2, 4]-dithiazolidine [hydrochloride]

Where, R= (a) Phenyl, (b) *o*-Cl-phenyl, (c) *m*-Cl-phenyl, (d) *p*-Cl-phenyl, (e) *o*-tolyl, (f) *m*-tolyl (g) *p*-tolyl.

3c: IR (KBr) :υ 3032.1 (Ar-H), 2769.7 (C-H aliphatic), 1593.2 (C=N), 1541.1 (C-C), 1131.0 (C-N), 1207.4 (C=S), 715.5 (C-S), 532.3 (S-S), cm^{-1}; ^1H NMR (δ in ppm, $CDCl_3$): δ 7.94-7.22 (8H, m),; δ 2.358-2.353 (3H, s, CH_3) Mass (m/z): 350 (M^+), 335, 315, 259, Anal. Calcd for $C_{15}H_{11}N_2S_3Cl$, HCl: C, 51.42; H, 3.14; N, 8.00; S, 27.42; Found: C, 51.46; H, 3.10; N, 8.04; S, 27.43.

Table -1: Physical data for characterization of compounds (3a-g)

Compd	Yield %	R_f	M.P. ^0C	Analysis (%): Found (calcd)	
				N	S
3a	78.00	0.65	122	8.90(8.86)	30.34(30.37)
3b	72.00	0.70	110	8.02(8.00)	27.38(27.42)
3c	68.00	0.50	101	8.04(8.00)	27.43(27.42)
3d	55.00	0.52	123	7.50(8.00)	27.38(27.42)

C and H analysis was found satisfactory in all cases.

Acknowledgement

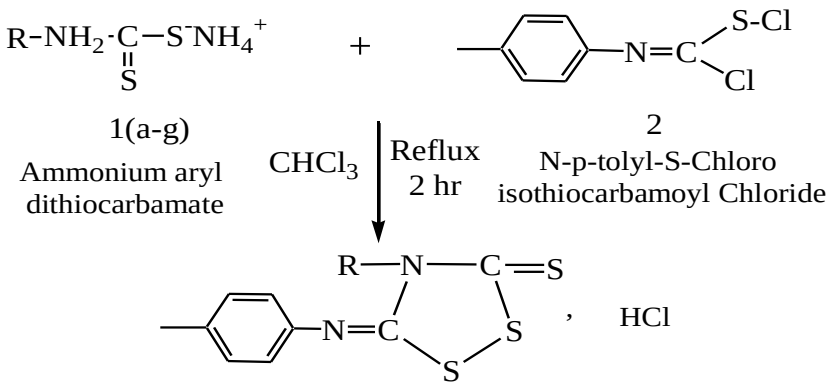
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Gaphical Abstract



3(a-g)

3-thio-4-aryl-5-tolyl-[1, 2, 4]-dithiazolidine [hydrochloride].

R= (a) Phenyl, (b) *o*-Cl-phenyl, (c) *m*-Cl-phenyl, (d)) *p*-Cl-phenyl,

(e) *o*-tolyl, (f) *m*-tolyl, (g)*p*-tolyl

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19

Characterization of Diesel Mixtures by Ultrasonic Methods

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Abstract: Petroleum fuel has a higher demand in the automobile sector. To meet this demand petroleum fuels are adulterated by some unwanted impurities. These impurities cause bad effects on fuel engines as well as the environment. To protect the environment and automobile engines; the detection of adulteration is important. The ultrasonic method is a recent technique for adulteration detection so the ultrasonic velocity method is used with physiochemical parameters for the characterization of Diesel.

Keywords: Diesel Mixture, Physiochemical characterization, ultrasonic method, Evaluation techniques

1. Introduction

Petroleum products have a lot of demand in the current market because of increasing automobile sectors to meet increasing demand for goods and public transport [1]. To meet this increasing demand there are some malpractices of adding adulterant in petroleum fuel and their presence can not be identified by simple visual inspection. But because of this adulteration, it is dangerous to the environment, human health as well as functioning of the engine. Therefore characterizing and determining its quality and being able to distinguish between these types is of utmost importance to protect the consumer as well as the environment. Adulteration of fuel becomes an acute problem today [2][3].

The ultrasonic method has recently used the Nondestructive method for the characterization of liquid fuel. Evaluation of petroleum fuel by ultrasonic method can be a better option. Density, viscosity, API gravity these physiochemical properties are of importance to characterize the different types of fuels but these are not sufficient to detect adulteration in fuel [3].

The objective of this study is to demonstrate the ability of ultrasonic methods to characterize petroleum products with physiochemical methods for detecting adulteration easily[4].

2. Materials and Methods

Diesel purchased from HP petrol pump. I have to study the adulteration of kerosene in diesel I purchased kerosene from the local market. The Kerosene purchased was blue. Both samples were kept in an airtight plastic tank. These diesel and kerosene were evaluated as per IP/ASTM norms. Then these results were compared with IS/ BIS norms for kerosene and diesel. Following Physiochemical characterization has been done on Diesel and kerosene samples.

- Density
- Specific Gravity
- API gravity
- Viscosity
- Ultrasonic velocity

2.1. Preparation of custom proportions of blends of fuel and adulterants

As an adulterated sample unwanted material is present in various amounts commonly in the range 20-80%. Hence the blends are prepared in such a way that it will cover the adulteration range. The blends are prepared as follows:

Sr. No.	% of kerosene	% of Diesel
1.	20	80
2.	40	60
3.	60	40
4.	80	20

Table 1. Percentages of Blends

These blends were kept in airtight bottles.

2.2. Evaluation of blends as per IP or ASTM norms:

The blended samples were subjected to various tests as per IP/ASTM norms such as Density, Specific Gravity, Viscosity, and ultrasonic velocity. Their tests have shown the variation in properties will indirectly indicate the quantity of adulterant in the sample.

3. Experimental Procedure:

The experimental procedure adopted for this experiment is given below

1) Specific gravity and API Gravity is calculated by the following formula

$$\text{Specific Gravity at } 25\ ^0\text{c} = \frac{Weight\ of\ sample}{Weight\ of\ distilled\ water} \text{ (for equal volume)}$$

API Gravity is calculated by the formula

$$\text{API} = \frac{141.5}{Sp.Gravity\ at\ 15.6} - 131.5 \text{ (Sp. Gravity is calculated at } 15.6^0\text{ c)}$$

2) Viscosity: The viscosity of the sample has been calculated by U – U-tube Viscometer.
3) Ultrasonic velocity measurement: Ultrasonic velocity has been measured by using Ultrasonic Interferometer. The formula used for measuring ultrasonic velocity is given below

Velocity = Wavelength × Frequency

Where velocity is measured for different blends. And Observations are given in Table 2.

3.1. Experimental Observations

Diesel with kerosene is evaluated as follows: All tests were done at 25^0 c.

Sample parameter	100% D + 0% K	80 % D + 20 %K	60 % D + 40 % K	40% D + 60 % K	20% D + 80 % K	0 % D +100 % K
Density	0.8322	0.8223	0.8222	0.8208	0.8181	0.7800
Specific Gravity	0.8336	0.8288	0.8187	0.8173	0.8146	0.7811
API Gravity	40.06	41.3140	41.3172	41.6289	42.1882	43.1992
Viscosity	4.35	2.93	2.73	2.59	2.47	2.38
Ultrasonic velocity	1325	1315.2	1281.6	1278.08	1277.4	1267.5

Table 2. Experimental Observation of Blends of Kerosene with Diesel

4. Results and Discussion

From the above experimental procedure, it is observed that, For the Kerosene diesel adulterated sample, as

A. As the percentage of adulterants increases density of diesel decreases.
B. As the percentage of kerosene increases in diesel, specific gravity also decreases.
C. As the percentages of kerosene increase API gravity increases.
D. viscosity decreases as the adulterant increases.
E. Ultrasonic velocity decreases as percentages of kerosene in diesel increases.

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20

Phytochemical and Proximate Analysis of Leaves of *Heteropogon Contortous* (L.) Beauv

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ABSTRACT :

Recently Proximate analysis and phytochemical analysis of *Heteropogon Contortous (L.) Beauv* from Wazzar Village,located in Achalpur tehsil of Amravati,Maharashtra.The leaves sample contained tannin, saponin, protein, steriods, terpenoids, carbohydrate,alkaloids, flavonoids.Proximate analysis of moisture, ash,crude fiber,crude Protein, solubility were check. The values of it is moisture (27.78%), cold water (64.4%), hot water (50.4%), 1%NaOH (51.76%), 1%HCl (54.57%), ash content (13.48%). These results indicate that the Heteropogon Contortous (L.) Beauv. contains nutrients elements that will be useful in nutrition. Also the existence of some phytochemicals like tannin, saponin and steroids illustrated medicinal action of the plant in its therapeutic uses. The result of their phytochemcial screening could justify the observed activities and validate their use in herbal medicine.

Keywords: Proximate composition, Phytochemical analysis, *Heteropogon Contortous (L.) Beauv*

INTRODUCTION :

The term “medicinal plants” includes various type of plants used in herbalism and some of these plants have medicinal activities. Medicinal plants are the “backbone” of traditional medicine, which means more than 3.3 billion people in the less developed countries utilize medicinal plants on a regular basis [1].

Medicinal plants are an integral component of research developments in the Pharmaceutical industry. Such research focuses on the isolation and direct use of active medicinal constituents, or in the development of semi-synthetic drugs, or still again on the active screening of natural products to yield synthetic pharmacologically-active compounds. Natural products play an important role in drug discovery process including the provision of basic compounds affording less toxic and more effective drug molecules, serve as extremely useful natural drugs, exploration of biologically active prototypes towards newer and better synthetic drugs and modification of inactive natural products by suitable biological or chemical means into potent drugs [2].

Spear grass (*Heteropogon contortus* (L.) Beauv. ex Roem. & Schult.) Is a tropical perennial grass. It grows to a height of 50 to 150 cm, is tufted and highly variable. Its stems are geniculated at the base, erect at their upper levels, often branched, particularly at flowering [3]. The leaves are green or bluish green, usually glabrous or with few long hairs at the base. The leaf-blade is folded when young, and then flat at maturity, 3-30 cm long, 2-8 mm broad, and somewhat canoe-shaped at the apex [3, 4]. The inflorescence is a 3 to 8 cm long raceme borne single or in pairs at the axil of the upper leaves. The spikelets are paired and very dissimilar according to their position on the raceme. Male or sterile spikelets are awnless, sessile and borne at the base of the raceme, or pedicellate and borne at the apex. Bisexual spikelets are only borne at the apex and they are all awned. The long awns (5-10 cm long) and the way they become twisted as the seeds mature are a characteristic trait of spear grass. The seed is a

caryopsis, 3.5-4.5 mm long, grooved and whitish in colour [3, 4, 5]. There were considerable numbers of local species and varieties in the early botanical literature. Only a few commercial varieties are available, for example "Rocker" from Arizona and "Kahoolawe" from Hawaii [4].Aside from phytoconstituent identification, it is also critical to analyze plants for their proximate and mineral compositions to expand knowledge of their nutritional health benefits. The review of the literature revealed that no previous work on the proximate analysis of Heteropogon Contortous (L.) Beauv. had been conducted.

MATERIALS AND METHODS

Collection of Samples

The leaves of the plant *Heteropogon contortus* (L) Beauv was collected from Wazzar Village,located in Achalpur tehsil of Amravati,Maharashtra., The whole plant was gently uprooted from the ground and then the leaves separated from the root after which they were dried at ambient temperature. The dried leaves were milled to fine powder, thereafter it was stored in an airtight container in the prior to its use.

Proximate analysis:

As per Aurveda, herbal drugs in the form of oral dosage are given to the patient as powdered materials mixed with water. For that, we performed proximate analysis to determine the physicochemical properties as well as solubility and nutrient content of herbal drug materials. Using a standard procedure and formula from the reported literature, the moisture content, ash content, crude protein, crude fiber, crude fat were determined.[6-8]

Moisture, ash and solubility were determined using the Association of official analytical chemists methods [5]. Crude fiber was estimated from the loss in weight on ignition of dried residue following digestion of fat-free samples.

Ash content:

An ignited and weighed silica crucible which contains 1gm of the powdered sample was incinerated slowly by raising the temperature in a muffle furnace at 450ºC for 4 – 5 hours. It was cooled in desiccators and weighed. The procedure was repeated until a constant weight was obtained. The percentage of total ash was calculated.

Moisture Content:

The oven-drying method was used to determine moisture. The weight of the empty crucible was recorded and kept in the oven for 1 hour at 1100C, then 1 gm of dried sample was placed in a crucible (W1) and kept in the oven for 1 hour at 1100C. It was then cooled and weighed until the weight remained constant (W2). The moisture content (%) was calculated.

Crude fiber content:

After extraction with petroleum ether, 5 g of the dry material was boiled with 2% H_2SO_4 and NaOH solution for 30 minutes, respectively. It was filtered and washed the residue with boiling water and dried for 2 hrs at 130^o C, cooled in a desiccator and weighed. Then the residue was ignited at 550 °C for 25 min. and cooled in a desiccator before reweighing.

Table -1

Sr.No.	Solubility in	Actual weight of sample taken in gm	Loss of wt. of sample in gm	%
1	Cold water	1.000	0.644	64.4
2	Hot water	1.000	0.504	50.4
3	Dil.NaOH	1.000	0.5176	51.76
4	Dil.HCl	1.000	0.5457	54.57
5	Ash Content	1.000	0.1348	13.48
6	Moisture Content	1.000	0.2778	27.78
7	Crude Fiber	---	---	33.7
8	Crude Protein	---	---	2.7

Phytochemical analysis :
Phytochemical analysis of the *Heteropogon contortus* (L) Beauv leaves.

S.No.	Content	Methanol	Aqueous
1	Amino Acids	-	-
2	Proteins	-	-
3	Carbohydrates	+	+
4	Saponins	-	+
5	Alkaloids	+	+
6	Phenols	+	+
7	Steroids	+	+
8	Terpenoids	+	+
9	Cardiac Glycosides	+	+
10	Flavonoids	+	+
11	Tannins	+	+
12	Anthroquinones	+	+

"+" = present, "-" = absent

RESULT AND DISCUSSIONS

The results of the proximate analysis support the use of the leaves as a food supplement. From the result, it was found that the total ash content obtained from dry leaves is 13%. Ash content is generally taken to be a measure of the mineral content of original food.The moderate moisture content provides for an activity of water-soluble enzymes and coenzymes needed for the metabolic activities of the plant. The total moisture content is 27.78 % .The proximate composition of the plant is depicted in table no.1.

The presence of flavonoids inferred that the leaves has the biological functions like antioxidant,allergies protection, free radical, inflammation, ulcers, hepatotoxins, tumor and viruses[8]. Flavonoids are water soluble free radical and antioxidants which prevent oxidative cell damage, and have strong anti-ulcer and anticancer activity[10]. Saponin content suggest that usefulness of the leaves as a productivity agent. The saponin level is low, either compared with the results from another works. Alkaloids are the most efficient medicinally
significant bioactive substances in plants. Alkaloids and the synthetic derivatives are used as medicinal agents because of their bactericidal and analgesic properties. Tannins healing of wounds and inflamed mucous membranes. This are water soluble phenolic compounds which precipitate proteins. They exist in all plants .Tannins add to proteins making them bio-unavailable [11]

CONCLUSION

This type of study will be applicable for the pharmaceutical, medicinal, agricultural, industrial and biochemical sciences. This study also shown that proximate, phytochemical analysi of *Heteropogon contortus* (L) Beauv leaves is a balanced and rich source of macro- and micronutrients. So the further study will be carry out on this plant.

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21

A Review of Computer-Aided Drug Discovery (CADD)

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ABSTRACT

Computer-aided drug discovery (CADD) is an innovative approach that leverages computational tools to accelerate and improve the drug development process. With the advancement of technology, CADD has become an increasingly prevalent tool in the pharmaceutical industry. By simulating and analyzing molecular interactions, predicting drug-target binding affinities, and screening vast libraries of compounds, CADD has proven to be instrumental in identifying potential lead compounds with therapeutic potential. Through its ability to efficiently sift through enormous amounts of data and generate accurate predictions, CADD enables researchers to prioritize the most promising candidates for further investigation, ultimately streamlining the drug discovery timeline and increasing the chances of successfully developing effective treatments for various diseases.

Keywords: CADD, QSAR, Molecular docking.

1. INTRODUCTION

Drug discovery is a complex and time-consuming process that involves the identification and development of new therapeutic molecules to treat various diseases. Traditionally, this process heavily relied on experimental methods, which can be expensive, time-consuming, and limited in their ability to explore vast chemical space. However, with the advent of computational chemistry, a powerful field at the intersection of chemistry, biology, and computer science, drug discovery has witnessed significant advancements. Computational chemistry employs computer simulations, algorithms, and mathematical models to accelerate the drug discovery process, offering valuable insights into the behaviour of molecules and their interactions with biological targets. This review provides an overview of the role of computational chemistry in drug discovery, explores the techniques and tools employed, discusses the challenges and limitations, and highlights the future perspectives and advancements in this exciting field.

Overview of the drug discovery process

We are probably wondering how new drugs are discovered. It's not as simple as mixing random chemicals in a lab and hoping for the best. No, it's a carefully orchestrated process that involves a lot of trial and error, and a pinch of luck. The drug discovery process typically starts with identifying a target, which could be a receptor or an enzyme involved in a disease pathway. Once the target is identified, scientists embark on a mission to find a molecule that can interact with this target and either enhance or inhibit its function.

Now, you're probably thinking, "Well, that sounds like a lot of work!" And you're right! But fear not, because this is where computational chemistry swoops in to save the day.

Computational chemistry is like the superhero of drug discovery, using powerful computer modelling techniques to predict the behaviour of molecules and their interactions with targets.

2. ROLE OF COMPUTATIONAL CHEMISTRY IN DRUG DISCOVERY

Computational chemistry brings a whole host of advantages to the drug discovery table. For one, it saves time and money. Instead of blindly testing thousands of molecules in the lab, scientists can use computational methods to screen and prioritize the most promising candidates. It's like having a crystal ball that tells you which molecules are worth pursuing. Another advantage is that computational chemistry allows scientists to explore a vast chemical space. They can virtually generate and test millions of compounds without ever stepping foot in a lab. It's like having a magical laboratory that's not constrained by physical limitations.

Integration of Experimental and Computational Approaches

Now, you might be thinking, "Well, if computational chemistry is so amazing, can we just replace all the lab work with computers?" Not quite. While computational methods are incredibly powerful, they're not infallible. They still need to be validated with experimental data to ensure accuracy. That's why scientists often employ an integrated approach, combining both computational and experimental techniques. By synergizing the powers of computational chemistry and good old-fashioned test tubes, they can accelerate the drug discovery process and increase the chances of success.

3. TECHNIQUES AND TOOLS IN COMPUTATIONAL CHEMISTRY FOR DRUG DISCOVERY

Structure-Based Drug Design

Structure-based drug design is like playing molecular Tetris. Scientists use the three-dimensional structure of the target protein to design molecules that fit into specific pockets or binding sites. It's all about finding the perfect shape and electrostatic properties that will allow the molecule to interact with the target desirably.

Ligand-Based Drug Design

Ligand-based drug design takes a different approach. Instead of focusing on the target protein, scientists analyse molecules that have already shown activity against the target. They then extract common features and create new molecules based on those patterns. It's like reverse engineering a recipe to create a delicious new dish.

Quantitative Structure-Activity Relationship (QSAR)

Ever wondered if there's a mathematical equation for drug discovery? Well, QSAR comes pretty close. It's a technique that uses statistical models to establish correlations between the structure of a molecule and its biological activity. By understanding these relationships, scientists can predict the activity of new molecules and prioritize those with the highest chances of success.

4. VIRTUAL SCREENING AND MOLECULAR DOCKING IN DRUG DISCOVERY

Virtual screening is like speed dating for molecules. It involves screening large libraries of compounds against a target protein to identify potential hits. Instead of physically testing each molecule, scientists use computer algorithms to predict how well they will interact with

the target. It's a quick and efficient way to narrow down the options and focus on the most promising candidates.

Molecular Docking Methods

Molecular docking is like playing a game of molecular lock and key. Scientists use computational algorithms to predict how a small molecule (the ligand) will bind to a target protein (the receptor). By exploring different orientations and conformations, they can determine the most favourable binding pose. It's like solving a puzzle where the reward is a potential new drug.

Validation and Analysis of Docking Results

Of course, docking results are not to be taken at face value. They need to be validated and analysed to ensure their reliability and relevance. Scientists use various techniques, such as scoring functions and experimental validation, to assess the quality of the docking results. It's like a reality check for those molecules that thought they were the perfect match. And there you have it; a whirlwind tour of how computational chemistry shakes things up in the world of drug discovery. It's a fascinating field that combines science, technology, and a dash of creativity to create new medicines that can change lives. So next time you hear about a groundbreaking drug, you can appreciate the superheroes behind the scenes, harnessing the power of computers to make it happen.

5. MOLECULAR DYNAMICS SIMULATIONS AND QUANTUM MECHANICS IN DRUG DISCOVERY

Role of Molecular Dynamics Simulations

In the world of drug discovery, scientists are turning to computational chemistry techniques such as molecular dynamics simulations to understand the behavior of molecules at the atomic level. By simulating the movements and interactions of molecules over time, researchers can gain valuable insights into how drugs interact with their target proteins. This knowledge is crucial for designing and optimizing drug candidates with higher efficacy and fewer side effects.

Quantum Mechanics Applications in Drug Discovery

Quantum mechanics, on the other hand, provides a more detailed and accurate description of molecular properties and interactions. It allows scientists to calculate properties such as molecular energies, electronic structures, and reaction mechanisms. This information is vital in understanding the fundamental aspects of drug action and can guide the development of more potent and selective drugs.

Combining Molecular Dynamics and Quantum Mechanics

To achieve even greater accuracy, researchers often combine molecular dynamics simulations with quantum mechanics calculations. This hybrid approach, known as QM/MM (quantum mechanics/molecular mechanics), takes advantage of the strengths of both methods. It allows for a more realistic and comprehensive representation of the drug-target interactions, taking into account the dynamic nature of the system and the quantum effects that are critical for understanding complex biological processes.

6. CHALLENGES AND LIMITATIONS OF COMPUTATIONAL CHEMISTRY IN DRUG DISCOVERY

Accuracy and Reliability of Computational Models

Despite the significant advancements in computational chemistry, there are still challenges when it comes to the accuracy and reliability of the models used in drug discovery. The accuracy of predictions heavily relies on the quality of the force fields, parameterization methods, and approximations employed. It is essential for scientists to constantly refine and validate these models against experimental data to ensure their reliability.

Handling Large Data Sets and Computational Complexity

Another challenge is the exponential growth of data in drug discovery. With the increasing availability of genomic, proteomic, and chemical data, computational chemists must develop efficient algorithms and techniques to handle and analyze these large data sets. Additionally, the computational complexity of modeling drug-target interactions requires substantial computational resources, which can be a limiting factor for many research groups.

Limitations in Predicting Drug Efficacy and Safety

Computational chemistry methods have their limitations in accurately predicting drug efficacy and safety. While they can provide valuable insights into drug-target interactions, they cannot capture the complexities of the human body fully. Factors such as metabolism, pharmacokinetics, and off-target effects still require experimental validation. Therefore, computational chemistry should be considered as a complementary tool rather than a standalone solution in drug discovery.

7. FUTURE PERSPECTIVES AND ADVANCEMENTS IN COMPUTATIONAL CHEMISTRY FOR DRUG DISCOVERY

Emerging Technologies in Computational Chemistry

Exciting advancements in computational chemistry are on the horizon. Techniques such as accelerated molecular dynamics, enhanced sampling methods, and machine learning-based approaches are actively being developed to overcome the limitations of current methodologies. These emerging technologies hold promise for more accurate predictions and deeper insights into drug-target interactions.

Integration of Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) are revolutionizing the field of drug discovery. By leveraging vast amounts of data, AI and ML algorithms can identify patterns, predict drug-target interactions, and even suggest novel drug candidates. The integration of these technologies with computational chemistry has the potential to significantly accelerate the drug discovery process and increase the success rate of developing new medications.

Potential Impact on Drug Discovery Process

The advancements in computational chemistry are poised to reshape the drug discovery landscape. By enabling faster and more accurate predictions, computational chemistry can help researchers prioritize potential drug candidates, optimize their properties, and reduce the need for extensive experimental screening. Ultimately, this can lead to a more efficient and cost-effective drug discovery process, benefiting patients worldwide by providing faster access to safer and more effective medications. In conclusion, computational chemistry has revolutionized the field of drug discovery, enabling scientists to expedite the identification and development of potential therapeutics with greater precision and efficiency. The integration of

computational methods with experimental approaches has proven to be a powerful combination, offering valuable insights into molecular interactions, structure-activity relationships, and drug efficacy. However, challenges such as accuracy, computational complexity, and the limitations of predictive capabilities still exist. Nonetheless, with the continuous advancements in technology, the future of computational chemistry in drug discovery holds immense promise. As researchers explore emerging technologies, incorporate artificial intelligence, and refine computational models, we can expect even greater strides in the discovery and development of novel drugs that improve the health and well-being of individuals worldwide.

CONCLUSION

The future of computational chemistry in drug discovery is promising. Emerging technologies such as artificial intelligence and machine learning are being integrated into computational chemistry workflows, allowing for more efficient and accurate predictions. Continued advancements in computational power and algorithms will further enhance the capabilities of computational chemistry. These advancements have the potential to revolutionize the drug discovery process, leading to the development of more effective and personalized therapeutics to address the unmet medical needs of patients.

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22

Synthesis and Anti-microbial Activity of Novel 3-[(3-substitutedamino-1,2,4-thiadiaz-3-yl)]amino-5-N-TAG-amino-1,2,4-thiadiazole [11b]

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Abstract
In this study new 3-[(3-substituted amino -1,2,4-thiadiaz-3-yl)] amino-5-TAG-amino-1,2,4-thiadiazole [11] were synthesized by the oxidative cyclization of 1-[S-TAG-N-substitutedthioamido] dicyanadiamide [8] and 1-[(N-TAG) thioamido]-5-substitutedformamidino-2-imino-4-thiobiuret [9] respectively in chloroform medium using liquid bromine as oxidizing agent. The newly synthesized compounds isolated in these reaction were characterized and justified on the basis of conventional elemental analysis, chemical characteristics, IR, NMR and Mass spectral analysis. The synthesized compounds were screened for antimicrobial activities by disc diffusion method.

Keywords – Synthesis, Dicyandiamide,Thiadiazol, Antimicrobial activity

Introduction

During last few decades, heterocyclic molecules containing nitrogen, sulfur and oxygen (five and six membered rings) have become the area of interest for medicinal chemists and researchers owing to their wide spectrum of biological/pharmacological activities.[1.] Thiadiazol, a five membered heterocyclic moiety containing one sulfur and two nitrogen atoms existing in four different isomeric forms, 1,2,3-thiadiazole; 1,2,4-thiadiazole and 1,2,5-thiadiazole and 1,3,4-thiadiazole has established its significant importance due to comprehensive pharmacological activities.[2-4.] 1,2,4-Thiadiazoles are heteroatom rich heterocycles with a vital role in medicinal chemistry programmes; many clinically approved pharmaceuticals contain this heterocycle.[5]

1,2,4-thiadiazoles are considered as most significant subclass of bioactive five-membered organic compounds for medicinal chemistry[6]and showed a remarkable biological activities such as cyclooxygenase inhibitors[7], human leukemia[8], antibacterial[9], antiulcerative[10], antihypertensive[11], cathepsin B inhibitors[12], anticonvulsant[13], antidiabetic[14], anti-inflammatory[7], and allosteric modulators[15.]

The wide range of application of 1,2,4- thiadiazols as pharmacophores in medicinal chemistry has attracted great interest in their synthesis.[16]

As a part of research work presently been undertaken in this laboratory for the synthesis of heteroacycles and heterocycles, it was thought interesting to investigate the oxidative cyclization of 1-[(N-TAG) thioamido]-5-substitutedformamidino-2-imino-4-thiabiuret [9] with liquid bromine in chloroform medium to obtain a novel series of 3-[(3-substitutedamino -1,2,4thiadiaz-3-yl)] amino-5-N-TAG-amino-1,2,4-thiadiazole [11] In this study, a new series of 1,2,4-thiadiazole derivatives (11a–e) were synthesized in good yields, and the structures of the compounds were confirmed by IR, 1 H-NMR, and elemental analysis. For that The newly synthesized substituted derivatives of thiocarbamide were screened for its antibacterial activities against some gram positive & gram negative pathogens. The compounds showed good & moderate activity against the pathogens.

Experimental

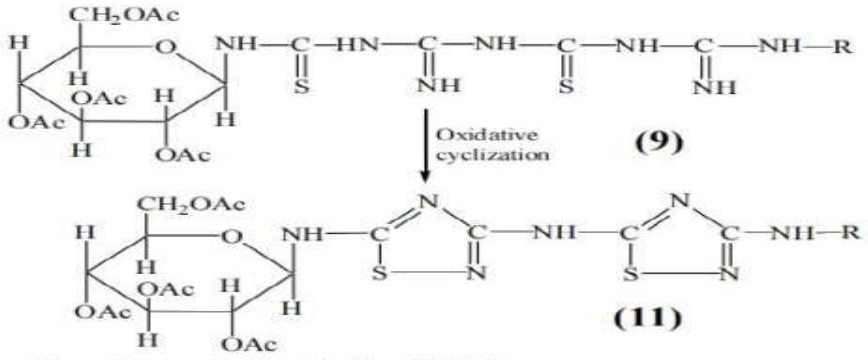
The melting points of all the synthesized compounds were recorded using hot paraffin bath and are uncorrected, The carbon and hydrogen analysis was carried out on Carlo-Ebra-1106 analyzer, nitrogen estimation was carried out on ColmanN-analyser-29. IR spectra were recorded on Perkin-Elmer spectrometer in the range 4000-400 cm-1 in KBr pellets. PMR spectra were recorded on Bruker AC-300F spectrometer with TMS as internal standard using CDC13 and DMSO-d6 as solvent. The FAB mass spectra were recorded on a Joel SX 102/Da-600 mass spectrometer/ Data System using Argon. The accelerating voltage was 10kV and spectra were recorded at room temperature by using m-nitro benzyl alcohol as a matrix. The purity of the compounds was checked on Silica Gel-G plates by TLC with layer thickness of 0.3 mm. All chemicals used were of AR grade.

Synthesis of 3-[(3-phenylamino-1,2,4-thiadiaz-3-yl)]amino-5-N-TAG-amino-1,2,4-thiadiazole [11b]

In china dish a paste of 1-[N-TAG thioamido]-5-phenylthio formamidino-2-imino-4-thiobiuret [9b] was prepared in chloroform. To this liquid bromine in chloroform was added with constant stirring. Initially the colour of bromine disappeared, the addition of bromine was continued till the colour of bromine persisted to the reaction mixture. The reaction mixture was allowed to stand for 8 Hrs. at room conditions. It is dark brown in colour. After the basification of the reaction mixture afforded brown coloured product, which on crystallization gave brown crystals of [11b] yield 61%, m. p.147^{0}C.

The probable reaction mechanism of the formation of [11b] may be stated as follows.

Scheme



Where R = -H, -phenyl, -methyl, -ethyl and allyl.

Similarly 3-[(3-Amino-1,2,4-thiadiaz-3-yl)]-amino-5-N-TAG amino-1,2,4-thiadiazole [11a], 3-[(3-methylamino-1,2,4-thiadiaz-3-yl)]-amino-5-N-TAG amino-1,2,4-thiadiazole [11c], 3-[(3-ethylamino-1,2,4-thiadiaz-3-yl)]-amino-5-N-TAGamino-1,2,4-thiadiazole [11d], 3-[(3-allylamino-1,2,4-thiadiaz-3-yl)]-amino-5-N-TAG amino-1,2,4-thiadiazole [11e] were synthesized from 1-[(N-TAG)thioamidino]-5-formamidino-2-imino-4-thiobiuret [9a], 1-[(N-TAG)thioamidino]-5-methylformamidino-2-imino-4-thiobiuret [9c], 1-[(N-TAG)thioamidino]-5-ethylformamidino-2-imino-4-thiobiuret [9d], 1-[(N-TAG)thioamidino]-5-allylformamidino-2-imino-4-thiobiuret [9e] in bromine in chloroform medium respectively

Result ad Discussion-

Spectral Evaluation-

The IR spectrum of compound 3-[(3-phenylamino-1,2,4-thiadiaz-3-yl)]amino-5-N-TAG-amino-1,2,4-thiadiazole was carried out in KBr pellets and is reproduce on plate No. IR-1. The IR spectrum clearly indicated the bands due to ν-NH, ν-C-H(Ar), ν-C=O, ν-C=N, ν-RC-N, ν-RC-S and an important absorption can be correlated in **Table No. 1.**

Table No.-1

Absorption	Assignment Observed	Absorption expected ($Cm^{-1)}$
3374.5	-NH- stretching	3500-3100
1695.8	-C=O stretching	1900-1600
1585.0	-C=N stretching	1789-1471
1213.0	-C-N Stretching	1200-1000
757.4	-C-S Stretching	800-600

The PMR spectrum of compound 3-[(3-phenylamino-1,2,4-thiadiaz-3-yl)]amino-5-N-TAG-amino-1,2,4-thiadiazole was carried out in DMSO-d6 and CDCl3 and shown in figure 2. This spectrum distinctly displayed the signals due to –NH protons at δ 9.5-8.6 ppm, Ar. Protons at δ 7.77 - 7.01 ppm.

The FAB mass spectrum of **3**-[(3-phenylamino-1,2,4-thiadiaz-3-yl)]amino-5-N-TAG-amino-1,2,4-thiadiazole [11b]was recorded at room temperature by using meta nitrobenzyl alcohol as the matrix m+ peak as well as other fragment peaks and the probable fragmentation pattern of the molecular ion.

Antimicrobial Activity

All the synthesized compounds were screened for antimicrobial activity using disc diffusion method[17] and all the pathogen tested during analysis are human pathogens. For this Whatman filter paper No. 1 disks of 5mm diameter were sterilized in autoclave and soaked in sample solution, blotted on sterile filter paper. 0.1ml of the inoculums of test organism was spread using sterile glass spreader on the surface of nutrient agar. The filter paper disks soaked in Gentamycin (20µg/ml) (Glaxo India Ltd.) and Ciprofloxacin (20µg/ml) (Glaxo smith kline) were used as positive controls and the filter paper disc soaked in dimethyl sulphoxide (DMSO) were used as a solvent. The compounds were taken at a concentration or 1mg/ml using dimethyl sulphoxide as a solvent .Fluconazole (20ug/ml)as a standard for antifungal activity. The inhibition zones were measured in millimeter by the end of the incubation period (24 hrs. at 37^0C for bacteria).

Table No-2

Compounds	**Inhibition zone in mm**					
	S.Typhi	***E.coli***	***P. aerogenosa***	***S.aurues***	***A.nigar***	***c.albicanes***
9a	8	8	-ve	-ve	9	-ve
9b	10	9	-ve	8	12	10
9c	9	9	7	7	10	10
9d	9	8	9	9	9	9
9e	10	9	10	9	12	12
DMSO	-	-	-	-	-	-
Fluconazole	-	-	-	-	12	12
Ciprofloxacin	10	9	10	9	-	-

From the results it is clear that compounds showed remarkable and considerable antimicrobial activity against organism. The activity of compounds were tested against all the pathogen by disc diffusion method. The antimicrobial activity of different compound against micro-organisms were examined in the presence study and their potency, were assessed by the presence or absence inhibition zone and zone diameter. The result are given in Table No. 2. From this table clearly indicates that, all the compounds are active against S. typhi, E.coli &A. nigar but some compounds 9a and 9b are inactive against P.aerogenosa, S.aurues & c.albicans.

Conclusion-

This paper reports the synthesis of 3-[(3-phenylamino-1,2,4-thiadiaz-3-yl)]amino-5-N-TAG-amino-1,2,4-thiadiazole [11b] & 3-[(3-Substitutedamino-1,2,4-thiadiaz-3-yl)]amino-5-N-TAG-amino-1,2,4-thiadiazole (11a-e) derivatives and characterization by FT-IR, PMR and mass spectrograph indicating formation of the desired product. The compounds were studied to evaluate in vitro antibacterial and antifungal properties by disc diffusion method. The antimicrobial activity of different compound against micro-organisms were examined in the presence study and their potency, were assessed by the presence or absence inhibition zone and zone diameter. From results, most of these compounds found to be potent antibacterial and antifungal agent exhibited comparable antibacterial and antifungal activity than the standard. It means that the compounds showed remarkable and considerable antimicrobial activity.

Acknowledgement: The author acknowledges the help of SAIF, CDRI, Lucknow for providing the spectral data. Authors are thankful to the Department of Chemistry, Mahata Fule College of Science Warud for providing the necessary facilities to carry out the research work & Dr.Rahul Bhagat (Biotechnolgy) for his help in doing antimicrobial activity.

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23

Sulfate promoted zirconia-based mixed oxide as solid acid catalysts for organic transformations

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Abstract:

After gaining attention by sulfated zirconia as solid acid catalyst, various modified versions of zirconia based catalysts have attracted attention due some extra properties associated with stability of the catalyst. Among these modified versions, various sulfate promoted zirconia-based mixed oxides have been reported in the literature, which includes SO_4^{2-}/ZrO_2-CeO_2, SO_4^{2-}/SnO_2-ZrO_2, SO_4^{2-}/TiO_2-ZrO_2, sulfated zirconia catalyst supported on mesostructured γ-Al_2O_3, sulphated mesoporous La_2O_3–ZrO_2 composite oxides, and many more. In this article, we have summarized some of the organic transformations catalyzed by sulfate promoted zirconia-based mixed oxides. These organic transformations includes Friedel-Crafts benzoylation of anisole with benzoyl chloride; dealkylation of 1,3,5-tri-*tert*butyl-benzene; synthesis of coumarins *via* Pechmann reaction; Mannich reaction between aldehyde, ketone and amines; synthesis of quinoxalines and synthesis of 2-aryl benzimidazoles and so on.

Keywords: Sulfate impregnation, sulfated zirconia, mixed oxide, organic transformations.

Introduction

Generally, liquid acid catalysts or homogeneous acid catalysts have been used to perform acid catalyzed reactions. Acid catalyzed reactions are efficiently carried out by these catalysts as these are soluble in the reaction medium and the reactant can easily reach to the active site of the catalyst and vice-versa. Whereas, some of these catalysts are very reactive and will not produce the product selectively. Further, the loopholes associated with the use of these systems are non-recoverable catalysts, tedious work-up procedures, and consequently responsible for pollution [1-5]. The scientific community was searching for a heterogeneous counterpart of these catalysts, that can work efficiently as a catalyst, gives high yield, recyclable, with easy and eco-friendly work-up procedure. In this regard, several heterogeneous catalysts such as zeolite, amberlite, nafion-H, molecular sieves, sulfated zirconia, and so on have been used as catalysts. Among these catalysts, sulfated zirconia is one of the important catalysts. It has been used extensively as a catalyst for processes/reactions such as alkylation, isomerization, cracking reactions, and several organic transformations [1-6]. In addition to this, many modified versions of sulfated zirconia can be used as catalysts. These modifications include different preparation procedures for sulfated zirconia catalysts, which can alter the properties of the catalyst. By using templated mesoporous, sulfated zirconia catalysts have been prepared. Other modification includes the use of MoOx or WOx as a promoter instead of SO_4^{2-} [7, 8]. Another important modification includes, sulfate impregnation of a mixed oxide of ZrO_2 with other metal oxide. In this article, we have discussed some of the organic transformation reactions, which are catalyzed by these sulfated zirconia-based mixed oxides.

Preparation of sulfated zirconia-based mixed oxides:

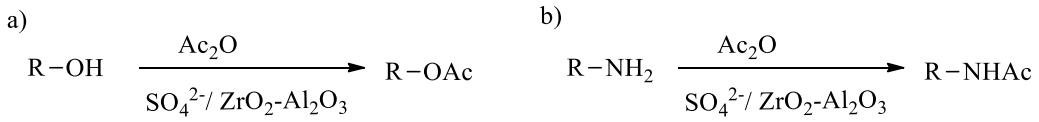
Several methods have been adopted in the literature for the preparation of sulfate impregnated zirconia based mixed oxides. These methods includes co-precipitation, sol-gel,

hydrothermal and so on. Reddy *et al.* prepared sulfated ceria-zirconia catalyst by co-precipitation followed by sulfated impregnation [9]. Ben Hamouda and Ghorbel used sol-gel method for preparation of sulfated zirconia supported by alumina [10]. Chakraborty *et al.* employed hydrothermal method for the preparation of silica sulphated zirconia [11]. These are some notable examples of use of different methods for synthesis of zirconia-based catalysts.

Organic Transformations by Sulfate promoted zirconia-based mixed oxide:

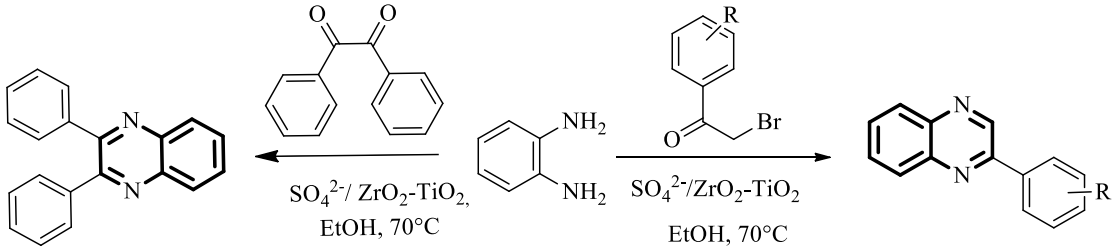
In this section, we have discussed some of the reactions reported by using sulfate promoted zirconia-based mixed oxide as a catalyst.

1. **Friedel-Crafts benzoylation of anisole with benzoyl chloride and dealkylation of 1,3,5-tri-*tert*butyl-benzene:**
   Zhao *et al*. have been prepared sulfated zirconia supported on mesostructured γ-Al_2O_3 as a catalyst used for Friedel-Crafts benzoylation of anisole with benzoyl chloride and dealkylation of 1,3,5-tri-*tert*butyl-benzene [12].
2. **Pechmann reaction and Mannich reaction:**
   Reddy *et al*. synthesized sulfate promoted CeO_2- ZrO_2 catalyst and utilized it for the synthesis of coumarins *via* Pechmann reaction as well as Mannich reaction between aldehyde, ketone and amines [9, 13].
3. **Acetylation of alcohols and amines:**
   Sulfate promoted Al_2O_3-ZrO_2 catalysts have been reported for acetylation of alcohol and amines with acetic anhydride (Scheme 1) [14].



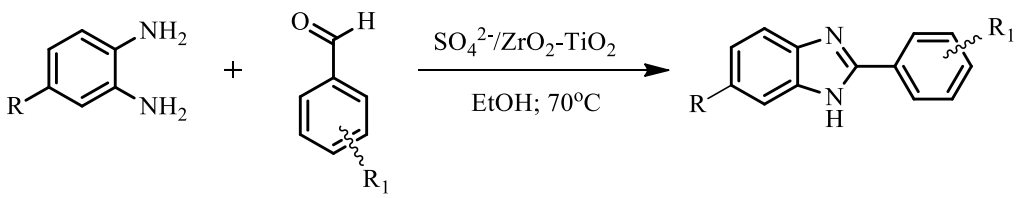
Scheme 1. Sulfate ZrO_2-Al_2O_3 catalyzed acylation of alcohols and amines.

4. **Synthesis of quinoxalines**
   Recently, Shelke *et al.* reported the synthesis of quinoxalines by reaction between phenacyl bromides/benzil and *o*-pheneylenediamine using sulfate promoted ZrO_2-TiO_2 as a catalyst (Scheme 2) [15].



Scheme 2. SO_4^{2-}/ZrO_2-TiO_2 catalyzed synthesis of quinoxalines.

5. **Synthesis of 2-aryl benzimidazoles**
   Furthermore, Shelke *et al.* have also been reported the synthesis of 2-aryl benzimidazoles by reaction of *o*-pheneylenediamines and different aromatic aldehydes (Scheme 3). This reaction is catalyzed by sulfate promoted ZrO_2-TiO_2 [16].



Scheme 3. SO_4^{2-}/ZrO_2-TiO_2 catalyzed synthesis of 2-aryl benzimidazoles.

Conclusion:

Sulfate promoted zirconia-based mixed oxides is a one of the promising group of catalysts in a family of solid acid catalysts. These catalysts have been used for variety of organic transformations. These catalysts are recyclable, easy work up procedures, promotes high yield, therefore it is an eco-friendly way to carried out many organic transformations such as Friedel-Crafts benzoylation of anisole with benzoyl chloride; dealkylation of 1,3,5-tri-*tert*butyl-benzene; synthesis of coumarins *via* Pechmann reaction; Mannich reaction between aldehyde, ketone and amines; synthesis of quinoxalines and synthesis of 2-aryl benzimidazoles. Furthermore, these catalysts can be explored for various other organic transformations.

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24

Structure, Physical and Chemical Properties of Thiourea with Their Derivatives

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Abstract:

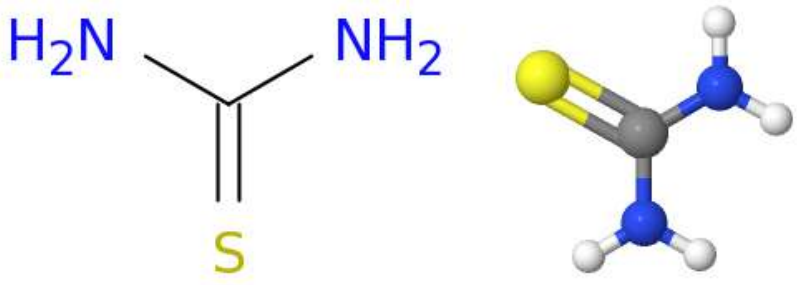
In this study six unsymmetrical thiourea derivatives, 1-isobutyl-3-cyclohexylthiourea (**1**), 1-*tert*-butyl-3-cyclohexylthiourea (**2**), 1-(3-chlorophenyl)-3-cyclohexylthiourea (**3**), 1-(1,1-dibutyl)-3-phenylthiourea (**4**), 1-(2-chlorophenyl)-3-phenylthiourea (**5**) and 1-(4-chlorophenyl)-3-phenylthiourea (**6**) were obtained in the laboratory under aerobic conditions. Compounds **3** and **4** are crystalline and their structure was determined for their single crystal. Compounds **3** is monoclinic system with space group $P2_1/n$ while compound **4** is trigonal, space group $R^3:H$. Compounds (**1**–**6**) were tested for their anti-cholinesterase activity against acetylcholinesterase and butyrylcholinesterase (hereafter abbreviated as, AChE and BChE, respectively). Potentials (all compounds) as sensing probes for determination of deadly toxic metal (mercury) using spectrofluorimetric technique were also investigated.

Keywords: thiourea derivatives, enzyme inhibition,

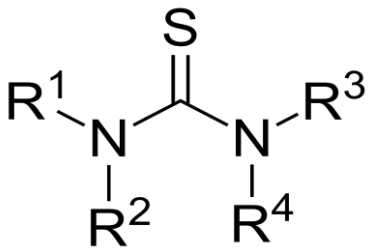
Introduction:

It plays an important role in the construction of hetero-cycles, the compounds formed by the insertion of one or more, similar or different hetero-atoms (other than carbon or hydrogen atoms) in different cyclic systems. It appears as white crystals which are combustible and in contact with fire give off irritating or toxic fumes. It acts as a precursor to sulphide to produce metal sulphides like mercury sulphide. Thiourea is a reagent in organic synthesis, a special branch of chemical synthesis, and is concerned with the construction of organic compounds via organic reactions. "Thioureas" can refer to a broad class of compounds with the general structure (R_1R_2N) (R_3R_4N) C=S. Thiourea is also called by names such as “Thiocarbamide, and Pseudo thiourea” Thioureas belong to thioamides, a functional group with the general structure R–CS–NR′R″, where R, R′, and R″ are organic groups. Examples include $RC(S)NR_2$, where R is methyl, ethyl, etc.

Structure of Thiourea molecule



Thiourea (CH4N2S)



Structure of Thiourea

Properties of Thiourea

- It is an organic compound containing sulphur atoms.
- Its molar mass is 76.12 $g.mol^{-1}$.
- It is a white-coloured compound.
- It exists in a solid state at room temperature.
- The melting point of thiourea is 176 – 178^{o}C.
- Its boiling point is 150 – 160^{o}C
- Its density is 1.405 $g.ml^{-1}$.
- It is highly soluble in water. For instance, 142 g of thiourea can be dissolved in one litre of water at 25^{o}.
- It is slightly acidic in nature
- Its crystals are highly combustible in contact with fire.
- It has pH value of more than 3.
- It is an odourless (with no smell) compound.
- Its surface tension is 1.04 10^{-2} N/m.
- Thiourea on heating above 130^{o} , forms ammonium thiocyanate. Upon cooling it again converts into thiourea.
- Reduction – Peroxides get reduced into their corresponding Diols (chemical compounds with two hydroxyl groups) by thiourea. During this reduction reaction, a by-product formed which is called endo-peroxide. Endo-peroxide is a highly unstable compound.
- Due to its non - volatile nature, it is also used in the ozonolysis of cyclic alkenes to give carbonyl compounds.
- It reacts with alkyl halides and forms thiols.

Uses of Thiourea

Total global production of thiourea approximately 40% is produced in Germany and another 40% in China. About 10,000 tonnes of thiourea is being manufactured globally in a year. Its bulk production clearly proves its significance in the market. Few of its applications are listed below:

- Thiourea Dioxide (prepared by oxidation of Thiourea with Hydrogen peroxide) is used as a reducing agent in many chemical reactions used in textile processing.
- It is used in the production of flame-retardant resins, which prevents or slows down the spread of fires.
- It is used as a source of sulphide, a compound of sulphur with another element. It reacts with alkyl halides and changes them into thiols, a sulphur analogue of alcohols that is simple it is an organic compound consisting of compounds with a sulphur atom. For example, ethane – 1,2 – dithiol is prepared by 1,2 – dibromoethane. The reaction is given below: $C_2H_4Br_2 + 2SC(NH_2)_2 \rightarrow [C_2H_4(SC(NH_2)_2)_2]Br_2$

$$[C_2H_4(SC(NH_2)_2)_2]Br_2 + 2KOH \rightarrow C_2H_4(SH)_2 + 2OC(NH_2)_2 + 2KBr$$

- Thiourea can be used as a source of sulphide in reactions with metal ions as well. For example, mercury sulphide is formed when mercury ion reacts with thiourea in presence of water and heat. The reaction is given below:

$$Hg^{2+} + SC(NH_2)_2 + H_2O \rightarrow HgS + OC(NH_2)_2 + 2H^+$$

- Thiourea condenses with - dicarbonyl and forms pyrimidine derivatives. It is used in vulcanization accelerators.
- It is used as an auxiliary agent.
- It is used in silver – gelatine photographic prints, diazo paper, light-sensitive photocopy paper, etc.
- It is used in many electroplating processes such as Clifton – Philips and Beaver bright electroplating, etc.
- For copper printed circuits, tin (II) chloride solution is used. Thiourea is also used in the solution.
- It is used in silver cleaning products such as Tarn x which contains thiourea, sulfamic acid and detergent.
- It is used in gold and silver leaching. Lixiviants are used for this purpose and thiourea is an important ingredient of these. Lixiviant is a liquid medium used in hydrometallurgy to selectively extract the desired metal from the ore or mineral.

- Even short exposure to the Thiourea causes severe irritation and temporary skin infection.
- 125mg/kg of thiourea can be deadly for rats on oral ingestion.
- On chronic exposure, thiourea can cause a goitrogenic effect on humans. Goitrogens can reduce the thyroid's ability to produce the hormones your body needs to function normally.
- Enlargement of the thyroid gland is known as goiter disease. In this disease, goitrogens disrupt the production of thyroid hormones. This stimulates the pituitary gland to release TSH and TSH promotes the growth of thyroid tissues.

Six Different Derivatives of Thiourea

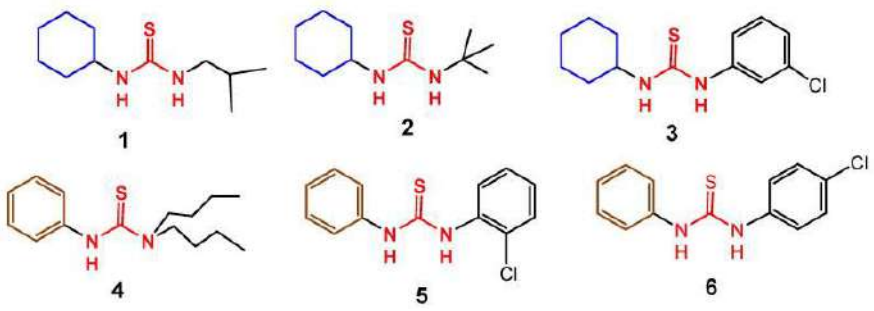


Figure 1: Structure of unsymmetrical thiourea derivatives, 1-cyclohexyl-3-(*iso*-butyl)thiourea (**1**), 1-cyclohexyl-3-(*tert*-butyl)thiourea (**2**), 1-cyclohexyl-3-(3-chlorophenyl)thiourea (**3**), 1-phenyl-3-(1,1-dibutyl)thiourea (**4**), 1-phenyl-3-(2-chlorophenyl)thiourea (**5**) and 1-phenyl-3-(4-chlorophenyl)thiourea (**6**) used in this study.

Material and Method:

All reactions were carried out under aerobic atmosphere and no special precautions were taken to exclude air or moisture during experiments. All chemicals were purchased from Vinit Chemicals, Nanded and were used without further purification. Thiourea derivatives described in this study are also commercially available in the marked, we reproduced them in the laboratory, they were obtained as crystalline material. The formation of compounds was confirmed with the help of available spectroscopic techniques, such as ATR-FTIR spectrometer and ^{1}H- and ^{13}C NMR spectra (in order to assist readers these data is provided below). Thiourea derivatives were prepared by reactions as previously reported [1,2].

Experimental Work

1.1. 1-cyclohexyl-3-isobutylthiourea, 1

Compound 1was synthesized by dropwise addition of cyclohexyl isothiocyanate (1 mL, 7.05 mmol) to isobutyl amine (0.7 mL, 7.05 mmol) in analytical grade acetone. The reaction mixture was allowed to stir over night at room temperature. The reaction led to the formation of precipitates and the progress was monitored by TLC. Solid material was separated from the mother liquor, washed with petroleum ether for removal of unreacted compounds and possible impurities. The solid was re-dissolves in ethanol and kept for slow evaporation. Spectroscopic datawere collected and structure of the desired compound was deduced.

Yield = 70 %; Molecular formula = C11H22N2S; m.p. = 102-105˚C; FT-IR(ATR): ν(cm−1) = 3431br (NH), 3214br (N-H), 2930s, 2850w (CH), 1617 (C=S), 1379 (NCN), 1448 (CSasy); 1
H-NMR (300 MHz, DMSO-d6) δ(ppm)= 0.85 (d, J(1H,1H) = 6.7 Hz, 6H, Me), 1.16, 1.25, 1.53, 1.63, 1.82 (overlapping multiplets of aliphatic protons), 3.18 (br, 1H, NH), 3.94(br,1H, NH). 13C-NMR (75 MHz, DMSO-d6) δ(ppm) = 20.1 (2C), 24.5 (2C), 25.1 (1C), 27.7 (1C), 32.3 (2C), 50.9 (1C), 51.6 (1C), 181.3 (C=S).

1.2. 1-cyclohexyl-3-(tert-butyl) thiourea, 2

In the similar manner as described above compound 2was prepared by mixing tertbutylamine (1 mL, 9.5 mmol) with a solution of cyclohexyl isothiocyanate (1.35 mL, 9.5

mmol) in dry acetone. Compound 2 was obtained as a colorless solid in ethanol.
Yield = 68 %; Molecular formula = C11H22N2S; m.p.= 138-140˚C; FT-IR (ATR): ν(cm−1) = 3421br, 3367br (N-H), 3050w, 2927w (C-H), 1636s (C=S), 1385 (NCN), 1544 (CSasy); 1HNMR (300 MHz DMSOd6) δ(ppm) = 1.03 (m, 2H, CH2), 1.20 (m, 4H, CH2), 1.61 (m, 4H,
CH2), 1.41 (s, 9H, Me), 1.83 (m, 1H, CH), 2.50 (p, 1H, CH), 3.16 (d, 1H, NH), 4.08 (br, 1H, NH); 13C-NMR (75 MHz, DMSO-d6) δ(ppm) = 24.4, 25.2, 29.0, 32.3, 50.6, 52.0, 180.2 (C=S).

1.3. 1-cyclohexyl-3-(3-chlorophenyl) thiourea, 3

A known amount of 3-chloroaniline (0.5 mL, 4.7 mmol) in 15 mL analytical grade acetone and equimolar amount of cyclohexyl isothiocyanate (0.6 mL, 4.7 mmol) was reacted together following the same method. Colourless crystals of 3were obtained in EtOH in few days, were separated from the mother liquor, FT-IR and NMR data were collected and suitable crystal of the compound was mounted for X-ray data collection and structure confirmation.
Yield = 66 %; Molecular formula = C13H17ClN2S, m.p. = 115-120˚C, FT-IR(ATR): ν(cm−1) 3295br, 3206br (N-H), 3060w (Ar, C-H), 2993w, 2849w (C-H), 1700s (C=S), 1534s (NCN), 1435s (CSasy); 1H-NMR (300 MHz, DMSO-d6) δ(ppm) = 1.26 (m, 4H, CH2), 1.67 (m, 4H, CH2), 1.92 (m, 2H, CH2), 1.99 (m, 1H, CH), 4.17 (br, 1H, NH), 7.10, 7.26, 7.31, 7.82 (m, m, m, m, 4H, CH, Ph),9.45 (br, 1H, NH); 13C-NMR (DMSO-d6) δ(ppm) = 25.0, 31.9, 39.8, 52.5, 121.0, 122.1, 123.5, 130.0, 132.9, 141.8, 179.5 (C=S).

1.4. 1-phenyl-3-(1,1-dibutyl) thiourea, 4

Phenyl isothiocyanate(1mL,8.3mmol) and dibutyl amine (0.88 mL, 8.3 mmol) in 20 mL acetone was treated as discussed above. Colourless crystals of the desired compound 4 were obtained in the same solvent at ambient temperature.
Yield = 95%; Molecular formula = C15H24N2S, m.p. = 85-87˚C; FT-IR (ATR 400-4000 cm−1) ν (cm−1) = 3700br (N-H), 2335w (C-H), 1529s (C=C), 1452s (NCN), 1205s (CSasy); 1HNMR (300 MHz, CDCl3), δ (ppm) = 0.96 (t, 6H, Me), 1.37 (m, 4H, CH2), 1.69 (pent, 4H, CH2), 3.65 (t, 4H, CH2N), 7.05(br, 1H, NH), 7.18, 7.31 (m, m, 5H, Ph); 13C-NMR (75 MHz, CDCl3) δ(ppm) = 13.7, 20.1, 29.4,51.4, 125.5, 125.6, 128.5, 139.8, 181.0 (C=S).

1.5. 1-Phenyl-3-(2-chlorophenyl) thiourea, 5

In the similar manner as described above by reacting 2-chloroanaline (0.87 mL, 8.3 mmol) with phenyl isothiocyanate (1 mL, 8.3 mmol), the product 5 was obtained as colourless crystalline solid by recrystallization from ethanol. In the whole reaction process, the
reaction was monitored by TLC until single spot product was formed.
Yield = 69 %; Molecular formula = C13H11ClN2S; m.p. = 90-92˚C; FT-IR (ATR) :ν(cm−1) = 3700br (NH), 2335w (C-H), 1528s (C=S), 1452s (NCN), 1442s (CSasy); 1H-NMR (DMSOd6) δ(ppm) = 7.16, 7.23-7.29, 7.32-7.39, 7.53, 7.63 (m, m, m, m, m, 9H, Aromatic protons), 9.43 (br, 1H, NH), 10.02 (br, 1H, NH); 13C-NMR (DMSO-d6) δ(ppm) = 123.8, 124.7, 127.2, 127.5, 128.6, 129.4, 129.8, 130.0, 136.4, 139.2, 180.3 (C=S).

1.6. 1-phenyl-3-(4-chlorophenyl) thiourea, 6

The derivative 6, was obtained as colourless solid by treating 4-chloroaniline (0.8 mL, 8.3 mmol) and phenyl isothiocyanate (1.0 mL, 8.3 mmol) in the same manner as reported

in literature [3]. Crystals were obtained in ethanol at room temperature by slow evaporation method.
Yield = 70 %; Molecular formula = C13H11ClN2S; m. p. = 95-99˚C; FT-IR (ATR): ν(cm−1) = 3436-3100br (N-H), 3000w (C-H), 1637s (C=S), 1549s (NCN), 1490s (CSasy); 1HNMR (DMSO-d6) δ(ppm) = 7.14, 7.37, 7.52 (m, m, m, 10H, Aromatic protons, NH), 9.88 (br, 1H, NH); 13C-NMR (DMSO-d6) δ(ppm) = 123.8, 124.6, 125.3, 128.3, 128.5, 138.5, 139.3, 179.3 (C=S).

3. NMR spectra of compounds 1–6

The 1H- and13C-NMR of all compounds were recorded on Bruker AM 300 MHz spectrometer. In the 1H-NMRspectra, all the aliphatic and aromatic protons appeared in their characteristic and expected region, 0.8-3.4 ppm and 7.0-7.9 ppm, respectively [4]. The NMR data analysis of all compounds reveal that the reaction is straightforward and no side reactions were observed. As each compound contains two types of N-H protons with different environment (except 4), and accordingly two signals were observed for each of them. The N-H proton close to aromatic ring was observed in up-field region while the other appeared in down-field region. From 13
C-NMR spectra of compounds 1-6, it is evidenced that all the aliphatic and aromatic carbons appeared below 50 ppm and 120-140 ppm, respectively. The chemical shift corresponding to C=S bond was noticed in the region of ≈180 ppm, the presence of this carbon in the spectra of compounds 1-6 provides enough justification regarding the formation and presence of thiourea derivatives. Other carbon atoms belong to molecules of respective compounds appeared in their characteristic regions.

Table S1. UV-Visible spectroscopic data of compounds 1–3, 5and 6.

Sr.No	Compound	Concentration (µg mL−1)	Scan range (nm)	λmax(nm)
1	**Comp -1**	**2**	200-400	296
2	**Comp - 2**		200-400	294
3	**Comp – 3**		200-400	298
4	**Comp -5**		200-400	294
5	**Comp - 6**		200-400	295

Result and Conclusion:

Compounds **1**–**6** are structurally very simple; they are accessible in the market and can also be obtained in laboratory under ambient conditions [5]. Compounds structurally analogous to **1**–**6** are good corrosion inhibitors in acidic medium [6] and show excited results in affording metal sulfides for useful applications [7]. Compound **5** has been used as starting precursors for the preparation of benzothiazole derivatives under catalyst free conditions [8]. There are several other reports wherein simple thiourea molecules after certain modifications have shown efficiency as bioactive compounds [9]. Compound **6** has already been used for its inhibitory activity against melanin B16 cells and mushroom tyrosinase and its synthesis has been reviewed [10,11]. The IC_{50} value as melanin B16 inhibitor was promising, 3.4 µM, while it exhibited moderate potency as mushroom tyrosinase inhibitor. The enzyme inhibition (AChE

and BChE) and metal sensing capability of compounds **1**–**6** (Figure 1) have not been reported so far. Since they are already in the field of bioorganic chemistry therefore these studies will help exploring their multidimensionality applications within a single system or organism whatever the case may be.

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25

Study of Proton and Metal-Ligand Stability Constants of hydroxy Substituted Chalcone Complexes pH-Metrically

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A B S T R A C T

In the present work, we have investigated the proton-ligand stability constants and metal-ligand stability constants of ligand 1-(5-bromo-2-hydroxyphenyl)-5-phenylpenta-2,4-dien-1-one (L_3) with transition metal ions like Cr (III) and Nd (III), which were determined pH-metrically at 0.1 M ionic strength. (30 ± 1^0C) in a 70% dioxane-water mixture by the Bjerrum method as adopted by Calvin Wilson. 1:1 and 1:2 complexes were formed between 1-(5-bromo-2-hydroxyphenyl)-5-phenylpenta-2, 4-dien-1-one (L3), Cr (III), and Nd (III). The values of pK and log k were evaluated and compared with the resultant data.

Keywords: Substituted chalcone, Dioxane – water mixture, stability constant.

1. Introduction

The stability constant, also known as the formation constant or association constant, is a measure of the strength of the bond formed between a ligand and a metal ion in a complex. It quantifies the stability or tendency of the complex to form and remain intact in a solution. Stability constants are determined through various experimental techniques, such as spectrophotometry or potentiometry. These constants are expressed as equilibrium constants and are typically denoted by the symbol K. The higher the stability constant, the more stable the complex is. Stability constants are important in various fields of chemistry, including coordination chemistry, biochemistry, environmental chemistry, and analytical chemistry. They play a crucial role in understanding the behavior of metal-ligand complexes in solution, their formation, and their potential applications.

The value of a stability constant depends on several factors, including the nature of the metal ion and ligand, the pH of the solution, temperature, and ionic strength. These constants provide valuable insights into the thermodynamics of complex formation and can be used to predict the stability of a complex under different conditions. Overall, stability constants are a fundamental concept in chemistry that helps to understand the formation and stability of metal-ligand complexes, and their importance extends to various areas of scientific research and applications.

A significant contribution was made to the field of stability constants of organic ligan ds and their metal complexes by Bjerrum[1] and Calvin[2]. The Schiff base N-[2-hydroxy-1-napthalydene]-2-methoxyanilline (3) was formed through condensation of 2-hydroxy-1-napthalydene with 2-methoxyanilline. It was studied for its formation of transition elements and its stability constants, with the order of stability constant being Cu > Ni > Zn > Mn > CO[3]. Jagtap's study examined the stability constant of Ni (II) with substituted pyrazole carboxylic acid derivatives at 298K in a 70% DMF-water mixture. [4] The stability constants of transition metals, including Cu (II) and Co (III) complexes with Schiff bases, were evaluated for anti-diabetic drugs. They were determined using the Calvin Bjerrum titration technique and

discussed in terms of order, ligand basis, and correlations. [5] Thakur et al. [6] studied the stability constant of Schiff bases with lanthanum using pH metric titration and the Calvin-Bjerrum method. They calculated thermodynamic parameters like Gibb's free energy change, entropy change, and enthalpy change. Thorat et al. [7] studied the complex formation between Pr (III) and Sm (III) metal ions and 3-(2-hydroxy-3-nitro-5-methylphenyl)-5-(3-nitrophenyl) isoxazoline, 4-chlorophenyl isoxazoline, and 2-furyl isoxazoline. The study investigated the interaction of metal ions with the organic ligand N-[(E)-(4-Hydroxy-3-methoxyphenyl) methylene] isonicotinohydrazide. The ligand was synthesized using an anti-mycobacterial agent and aromatic aldehydes. The formation of these ligands was confirmed through various tests, with the stability constants arranged in a specific order. [8] The stability constants and thermodynamic parameters of transition metal complexes of substituted aminothiazole Schiff bases have been studied by R.P. Giram et al.[9]

2. Experimental methodology

2.1Material and Methods

All chemicals used are AR-grade. The ligand (L_3) was synthesized in the laboratory by the reported protocol[10]. The stock solution of the ligand was prepared by dissolving the required amount of ligand in a 70% (dioxane and water) mixture.

2.2 General procedure

Types of Titrations

i) Free acid HNO_3 (0.01 M)

ii) Free acid HNO_3 (0.01 M) and ligand (20 x 10^{-4}M)

iii) Free acid HNO_3 (0.01 M) and ligand (20 x 10^{-4}) and metal ions (4 x 10^{-4}M) against a standard 0.1N NaOH solution. The ionic strength of all the solutions was maintained at 1M by adding the appropriate amount of KNO_3 solution. All the titrations were carried out in a 70% (dioxane and water) mixture, and the readings were recorded for each 0.1 ml addition. The graph of the volume of alkali added (NaOH) against pH was plotted. The ligand involved in the present work may be considered a monobasic acid having only one dissociable H+ ion from the phenolic OH group, and it can therefore be represented as HL. The dissociating equilibrium can be shown as.

$HL \rightleftharpoons H^+ + L^-$

By the law of mass action, we have,

$K = [HL] / ([H^+] [L^-])$ (1)

Where, the quantities in bracket denote the activities of the Species at equilibrium.

3. Result and Discussion

3.1 Calculation of Proton-Ligand Stability Constant (n_A)

The plots between the volume of NaOH and the pH of the solution were used to determine the proton ligand stability constant (representing the replacement of H+ ions from the functional group of the ligand with respect to the pH value). The horizontal difference (V_2-V_1) was measured accurately between the titration curves of free acid and acid + ligand. It was

used to calculate the formation number n at various pH values and a fixed ionic strength μ = 0.1 M using Irving and Rossotti's equation [1, 2].

$$\bar{n}_A = \gamma \frac{(E_0+N)(V_2-V_1)}{(V_0+V_1)TL^0} \quad (2)$$

Where V^0 is the initial volume of the solution. E^0 and T_L^0 are the initial concentrations of the mineral acid and ligand, respectively. V_1 and V_2 are the volumes of alkali of normality N during the acid and ligand titration at a given pH. γ is the replaceable proton in the ligand. The data on n_A obtained at various pHs, along with the horizontal difference for some representative systems, are represented in Table 1. The metal ligand ligand formation number (n) is estimated by Irving-Rossotti's equation.

$$\bar{n} = \frac{(E_0+N)(V_3-V_2)}{(V_0+V_2)Tm^0} \quad (3)$$

Where the notations have the same meaning as given in the earlier equation. The horizontal difference (V_3-V_2) between the metal complex (A+M+L) and reagent (A+L) curve is used to evaluate the value of n using Irving Rossotti's equation.

Table 1 Proton ligand stability constant (pK)

Ligand	System	pK	
		Half integral method	Point wise method
L3	1-(5-bromo-2-hydroxyphenyl)-5-phenylpenta-2,4-dien -1- One	7.7871	6.4506

Table 2: Metal-ligand stability constant (log K)

System	$LogK_1$	$LogK_2$	Δ LogK
Cr (III)+L_3	5.7419	3.3126	2.4293
Nd (III)+L_3	5.5310	3.5278	2.0032

Conclusion

From the titration curves, it is observed that the departure between the acid-ligand (A+L) curve and the acid-ligand-metal (A+L+M) curve for all systems started at pH 3.6. This indicated the commencement of complex formation. Also, the change in color from yellow to

orange in the pH range from 3.9 to 8.6 during titration showed the complex formation between metal and ligand.

The difference between $LogK_1$ and $LogK_2$ is less than 2.5, indicating the simultaneous formation of 1:1 and 1:2 complexes. When the difference is greater than 2.5, a stepwise complex formation takes place. [11]. From Table 2, it is observed that in the all systems Cr (III)-L3 and Nd (III) + L3, the difference between log K_1 and log K_2 is sufficiently small, which indicates the simultaneous formation of complexes between metal ions and ligands takes place.

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26

Ecofriendly synthesis and characterization of Ethyl 2-imino-6-methyl-4-substituted phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate compounds

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Abstract: Ethyl acetoacetate, substituted aromatic aldehyde, and guanidine were the three components of a one-pot, three-component reaction that produced ethyl 2-imino-6-methyl-4-substituted phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate compounds [4a-c]. The reaction is effectively supported to provide the intended products, typically in high yields and within a brief timeframe. The newly synthesized chemicals structures were clarified by elemental and spectrum investigations. Using TLC, the purity of each compound was ascertained.

Keywords: Pyrimidine, Guanidine.

1. Introduction:

Heterocycles that include nitrogen are of synthetic importance since they belong to a significant class of both natural and artificial compounds, many of which have shown beneficial biological activity. the fascination with six-membered structures with two nitrogen atoms at positions one and three. In heterocyclic synthetic chemistry, the One Pot Multicomponent Reactions (MCRs), in which several reactions occur often in a single synthetic operation, have been heavily employed to generate carbon-carbon bonds. Similar reactions provide a multitude of options for efficiently building relatively complex molecules in a single phase of the process, so avoiding the laborious purification processes and allocating savings of both reagents and solvents. For this reason, understanding their biological conditioning and therapeutic applications is crucial for scientists working on drug discovery processes[3]. We have conducted the reactions in water, which is notable for its use as a non-flammable, non-hazardous, and green medium, based on the principles of green chemistry.

Pyrimidines have biological significance that motivates researchers to work on them. These activities include analgesic[1,2,9], antimicrobial activity[3,4,7] , anticonvulsant[5], antioxidant activity[5], antimycobacterial[6], antitumor[7], antiviral[8], anticancer[9,10] and antifolate[10].

2. Material and methods:

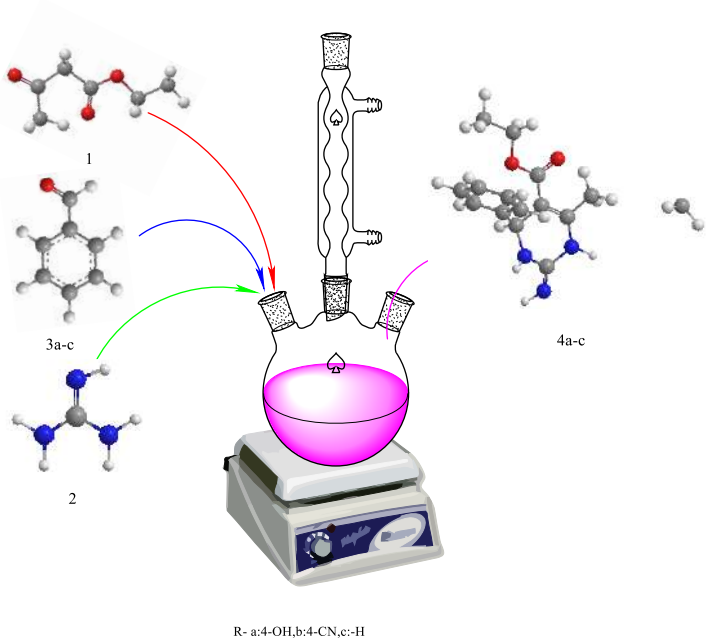
An uncorrected melting point was determined using open capillary tubes. Using an FTIR Agilent Technologies spectrometer at 4000-650, the FTIR spectra were recorded. Using tetramethyl silane (TMS) as an internal reference and d6-DMSO/CDCl3 as the solvent, the 1H NMR spectra were recorded on a Bruker spectrophotometer operating at 500 MHz. The units of chemical changes were ppm. We bought all of the solvents and reagents from Sigma Aldrich Chemicals Pvt Ltd. To maximize the reaction's purity and completeness, TLC was employed.

2.1 Synthesis Process in General:

2.1.1 Synthesis of phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate by ethyl 2-imino-6-methyl-4 substitution[4a-c]:

Substituted aromatic aldehyde (0.01mol), ethyl acetoacetate (0.01mol), and guanidine (0.01mol) were added to 15 ml of distilled water in a dry 50 mL round-bottom flask, and the mixture was manually agitated for two minutes. The reaction mixture was then heated for an

hour at 90 degrees Celsius in a water bath. A solid began to deposit as the reaction went on, and an hour later the flask was full with solid. Using a spatula, the solid was carefully removed from the conical flask. One milliliter of cold water was used to wash the yellow solid. From ethanol, the crude product was recrystallized to remove impurities.



Scheme-1

3. Physiochemical and analytical data for compounds:

3.1 Ethyl 4-(4-hydroxy phenyl)-2-imino-6-methyl-1, 2, 3, 4-tetra hydro pyrimidine-5-carboxylate(4a):

M.F: $C_{14}H_{17}N_3O_3$. M.W:278. M.P: 124–126 ^oC. Yield: 77.35%. FT-IR: 1510(Ar-C=C),1631(C=N), 1715(C=O), 2887(C-H), 3199(N-H), 3402(Ar-OH). ^{1}H-NMR (500 MHz, DMSO d_6, δ ppm): 7.81(s, 1H, =N-H), 6.91-6.71 (Ar-H), 4.50(S, 1H, R_2-NH), 4.03(q, 2H, -CH_2), 1.25(t, 3H, -CH_3), 2.27 (s, 3H, Ar-CH_3), 9.1 (s, 1H, Ar-OH). Anal. Calcd. (in %): C, 61.07; H, 6.20; N, 15.21. Found: C, 61.11; H, 6.281; N, 15.35.

3.2 Ethyl 4-(4-cyano phenyl) -2-imino -6-methyl-1, 2, 3, 4-tetra hydro pyrimidine -5-carboxylate(4b):

M.F: $C_{15}H_{16}N_4O_2$. M.W:285. M.P: 112–114 ^oC. Yield: 76.81%. FT-IR: 1502(Ar-C=C), 1628(C=N), 1714(C=O), 2265(Ar-CN), 2888(C-H), 3195(N-H). ^{1}H-NMR (500 MHz, DMSO d_6, δ ppm): 7.81(s, 1H, =N-H), 7.76-7.28 (Ar-H), 4.48(S, 1H, R_2-NH), 4.02(q, 2H, -CH_2), 1.20(t, 3H, -CH_3), 2.19(s, 3H, Ar-CH_3). Anal. Calcd. (in %): C, 63.39; H, 5.45; N, 19.83. Found: C, 63.35; H, 5.63; N, 19.69.

3.3 Ethyl 2-imino-6-methyl -4-phenyl-1, 2, 3, 4-tetra hydro pyrimidine- 5-carboxylate(4c):

M.F: $C_{14}H_{17}N_3O_2$. M.W: 260. M.P: 112–114 ^oC. Yield: 73.80%. FT-IR: 1509 (Ar-C=C), 1628(C=N), 1717 (C=O), 2882(C-H), 3199(N-H). ^{1}H-NMR (500 MHz, DMSO d_6, δ ppm): 7.81(s, 1H, =N-H), 7.28-7.17 (Ar-H), 4.59 (s, 1H, R_2-NH), 4.12 (q, 2H, -CH_2), 1.20 (t, 3H, -CH_3), 2.31 (s, 3H, Ar-CH_3). Anal. Calcd. (in %): C, 64.79; H, 6.59; N, 16.25. Found: C, 64.15; H, 6.29; N, 16.89.

4. Conclusion:

The main focus of this research work was pyrimidine derivatives have been synthesized based on green chemistry principles (multicomponent synthesis) using water as a solvent. The structures of synthesized compounds were confirmed by FTIR, 1HNMR and elemental

analysis. The reaction is effectively supported to provide the intended products, typically in high yields and within a brief timeframe

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27

Effect of Fe Dopant on Structural & Electrical Properties of Copper Oxide Nanoparticles

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Abstract: Nanocrystalline Copper oxide (CuO_2) was synthesized by sol-gel citrate method. Further it was modified by doping Fe in it. Structural and Electrical study was carried out for modified and unmodified CuO_2. From X-ray diffraction (XRD) studies it was observed that when CuO_2 doped with 2% Fe its Average Crystallite Size Increases from 41.32 nm to 54.51 nm on further doping with 0.1% & 0.3% Fe Its Average Crystallite Size decreases to 34.15 nm& 31.35 nm respectively. The electrical study of the nanocrystalline Copper Oxide is checkedfor different doping amount and also at different temperature for every sample. From the studyit is observed that, conductivity changes with the concentration of dopant and also varies withtemperature.

Keywords: Copper oxide, X-ray diffraction, crystallite size, Electrical Properties & Conductivity.

28

Preliminary Phytochemical Studies of *Cesalpinia crista* L.

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Abstract:

Caesalpinia crista L. belongs to Fabaceae and commonly known as 'sagargoti' in Marathi. It is widely employed across the Asian and African continent for treatment of various kinds of diseases and disorders like abdominal pain, amenorrhea, cystic fibrosis, diabetes, leucorrhea, malaria fever, rheumatoid arthritis. The aim of present study was to investigate the presence of phytochemicals of root, stem, leaf and fruit of *Cesalpinia crista* L. Ethanol, acetone, hexane and petroleum ether extract of selected material were screen for the presence of different secondary metabolites, it revealed the existence of alkaloid, steroids, phytosterol, tannin, flavonoids, and glycosides. The findings of the present study provided evidence that crude organic solvent extracts of *Caesalpinia crista* L. contain medicinally important bioactive compound, it justifies their use in traditional medicines for the treatment of various kinds of diseases.

Key words: *Caesalpinia crista* L., organic solvents, phytochemicals

Introduction:

Caesalpinia crista L. an important medicinal plant belongs to Fabaceae (Caesalpiniaceous), different parts of *C. crista* has several traditional medicinal applications and health benefit effects *C. crista* generally presents in tropical areas and found almost in every part of India and Pakistan **(Bhanderi, *et al.*, 2022).** Root, leaves, seed and bark is used in the treatment of different kinds of diseases such as pulmonary tuberculosis, malaria, pneumonia, colic fever, intermittent fever, swelling, menstrual complaints, skin diseases, tonic and as a uterine stimulant, to cleanse uterus and also alleviates edema and abdominal pain during this period. Various plant parts of *C. crista* traditionally used as antipyretic, periodic, tonic and vesicant for the treatment of backache, constipation, skin diseases, gynecological disorders, piles, ulcers and rheumatism **(Suryawanshi and Patel, 2011; Patil, K. S. 2005).**

The extracts different parts of *C. crista* have been reported to have anthelmintic activity antimalarial activity, antioxidant activity, anti-amyloidogenic, nootropic activity and cytotoxic activity **(Sadiya Afreen *et al.*, 2016).** Literature on *C. crista* revealed presence of different compounds and most of them belong to diterpenes group. Several traditional medicinal plants have been reported to have strong antimicrobial properties and some of them have already been used in the treatment of animals and people suffering from viral infection (**Mandal, *et al.*, 2011**).

Many plant and herbs that have potential as novel antiviral agents have been reported and wide spectrum of active secondary metabolites including alkaloids, coumarins, flavonoids, furyl compounds, lignans, polyphenolics, sulphides, saponins, terpenoids, thiophenes, proteins and peptides have been identified (**Srinivasa *et al.*, 2003**). The decoction of *Caesalpinia crista* root has been used for its significant health benefits to treat rheumatism, backache and as a tonic. In Ayurveda Indian Medicine System heartwood is bitter, astringent, constipating,

hemostatic and sedative and it is useful in the treatment of burning sensation, convulsions, diabetes wounds, diarrhoea, dysentery, epilepsy, leucorrhoea, leprosy, menorrhagia, haemorrhages, ulcers, skin diseases, (**Kirtikar and Basu,1989**).

Caesalpinia crista is a large woody climber height up to 15 m grows mainly on the river bank in tidal forests near eastern seacoast from Orissa and western sea coast from Konkan southwards and grown throughout India up to 800 meters elevation**.** Branches are finely grey-downy, armed hooked and straight hard yellow prickles on them. Bark is black, branchlets are glossy with recurved prickles. leaflets; 2-3 pair coriaceous, acute or obtuse, ovate or elliptic, upper surface shining, lower dull large, leaves bipinnate with recurved prickles at the base of pinnae, 2-5 pairs, often armed. Seeds of the plant are round, dry and hot, up to 1.2 cm in length, protected in a glossy yet very hard coat that may be green or ash gray in color, surface of the kernel is ridged and is furrowed and is about 1.23-1.75 cm in diameter (**Preedy *et al*., 2011; Pooja Upadhyay *et al*., 2019**).

Materials and Methods

Collection and Identification of materials:

The plant material i.e. roots, stem, leaves and fruits of *Caesalpinia crista* L., were collected from the botanical garden of Bapumiya Sirajoddin Patel Arts, Commerce and Science College, Pimpalgaon Kale, Tq. Jalgaon (Jamod), Dist. Buldhana – Maharashtra. The samples were collected during the year 2022-23. The Herbarium of *Caesalpinia crista* L., was prepared and authenticated from Department of Botany, Vidnyan Mahavidyalaya Malkapur. The root, stem and leaves were washed and kept for shade drying for 7-8 days or till it get the constant weight, whereas mature fruit was shade dried till get the constant weight. The fine powder of selected material were prepared with the help of mortle and pistle and finely powdered with the help of electric mixture grinder, prepared powder were stored in air tight container bottles at room temperature until used. 5 gram of the plant material powdered was wrapped in whatmann filter paper and placed in 100 ml beaker and selected solvent such as Ethanol, acetone, hexane and petroleum ether were added in each beaker and kept for overnight. Then extract was filtered through whatman filter paper and used for the detection of various phytochemical analyses.

Test for Phytochemicals

- **Alkaloids:** 2 ml of extract, few drops of Mayers reagents was added, white precipitate indicates existence of alkaloids.
- **Flavonoids:** To 2 ml of extract was taken, 10% of lead acetate was added, yellow precipitate indicate the presence of flavonoids.
- **Steroid**: 2 ml plant extract was taken in a test tube; 2 ml of CCl_3 and few drops of conc. H_2SO_4 were added in it and stir well. Chloroform layer appearance red and acid layer showed the greenish yellow florescence which indicated positive test for of steroid.
- **Glycosides:** 3 ml of extract, 4 ml of CCl_3 was added and stir well. The chloroform layer was separated then added 10% ammonium solution. The formation of pink colour indicate the presence of glycosides.
- **Carbohydrates:** About 0.5 ml of the extract was taken in which 0.5 ml of Benedict's reagent was added. The mixture was heated for 3 minutes in a boiling water bath. Appearance of red precipitate indicates the presence of carbohydrates.
- **Proteins:** 2 ml of extract, 2 ml of Millons reagent was added. White precipitates indicate the presence of proteins.

- **Amino acid:** 2 ml of extract, few drops of nitric acid was added. The existance of yellow colour it indicates the presence of protein and free amino acids.
- **Oil:** Small quantity of the extract was taken and pressed between two filter papers. Formation of spot indicates presence of oil.
- **Phenol:** About 4 ml of extract and 3 ml of 10% lead acetate solution was added .The formation of bulky white precipitate shows presence of phenol.
- **Tannins:** 5 ml of extract was taken and few drops of 5% $FeCl_3$ solution was added .The formation of dark green colour shows presence of tannins.
- **Saponins:** 0.5ml extract was vigorously shaken with few ml of distilled water. The formation of forthing is shows presence of saponins.
- **Terpenoids:** Salkowski's test- To 4 ml of plant extract, 2 ml of CCl_3 and 3ml Conc. H_2SO_4 were added carefully to form a layer, reddish brown colour of the inner face indicate the presence of terpenoids **(Thimmaiah, S. R. 1999; Yadav and Agrwal, 2011; Shailaja J. R. 2015; Sridhar et al., 2016).**

Observations and Results:

The phytoconstituents were extracted by using different solvents of increasing polarity like hexane, acetone, petroleum ether and ethanol. The Table 1 is representing the presence and absence of different phyto-constituents. Root, stem, leaf and seed extract of selected solvent revealed the presence of alkaloids, carbohydrate, protein and amino acids. Fruit extract shows the existence of oil. Glycosides were detected in root, stem, leaf and fruit. Stem extract shoed the presence of phenol where as other parts showed negative test for phenol. Tannin, flavonoids, saponins, steroids, terpenoids were detected in all selected parts of *C. crista* in different solvents.

Table no: 1. Preliminary phytochemical screening of *Caesalpinia crista* L.

Sr. no.	Primary metabolites	Root				Stem				Leaf				Fruit			
		E	A	H	P	E	A	H	P	E	A	H	P	E	A	H	P
1.	Carbohydrates	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2.	Proteins	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3.	Amino acid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4.	Oils	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+
5.	Glycosides	+	-	-	+	-	+	+	-	-	-	+	+	+	+	+	-
6.	Alkaloids	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7.	Phenol	+	-	+	-	-	-	-	-	-	+	+	-	-	+	+	-
8.	Tannins	+	-	-	+	-	-	+	-	+	-	-	+	+	-	-	+
9.	Flavonoids	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
10.	Saponins	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
11.	Steroids	+	-	+	-	-	+	-	-	+	-	+	-	+	-	+	-
12.	Terpenoids	+	-	-	-	+	+	-	-	-	+	-	+	+	-	-	+

(A-Acetone, E-Ethanol, H-Hexane, P- Petroleum ether)

Conclusion:

It is concluded from the present results that, root, stem, leaf and fruit of *C. crista* in different solvent extract revealed the existence of various secondary metabolites. The medicinal properties such as activity antimalarial activity, antioxidant activity, anti-amyloidogenic, of burning sensation, convulsions, diabetes wounds, diarrhea, dysentery, epilepsy, leucorrhea, leprosy, menorrhagia, hemorrhages, ulcers, skin diseases and cytotoxic activity etc. are due the presence of various secondary metabolites. Hence isolation of individual compound from the *C. crista* may found a novel drug.

Acknowledgement:

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29

Removal of Methylene Blue using *Cajanus Cajan* Activated Carbon

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Abstract
Research is required to explore and test new and new low cost materials for removal of Methylene Blue. In the present research article, generation of activated carbon derived from *Cajanus cajan* pericarp, an agricultural waste product, followed by its characterization using modern techniques like FTIR and SEM studies have been reported. This newly obtained activated carbon has been tested to estimate its practical applicability for removal of methylene blue from aqueous solution. Batch adsorption experiments were performed for this purpose. The influence of pH, contact time, adsorbent doses and initial methylene blue concentration have also been studied and reported. The results revealed that the activated carbon adsorbent reported in this article is effective for removal of methylene blue from wastewater, and thus can be successfully used for control of methylene blue pollution.
Keywords: methylene blue, activated carbon, Cajanus cajan, adsorption isotherm.

Introduction-In water sources occurrence of synthetic dyes gives hazardous effects to aquatic organism and human health when discharge directly to environment. More than 10,000 dyes have been widely used in textile, paper, rubber, plastics, leather and cosmetic, pharmaceutical, and food industries[1].The dyes consist of poisonous and complex components with slow degradation rate. Furthermore, the presence of dyes components affects the undesirable color change in water system. The unfavorable impact is not only from esthetics point of view but also from the decline of sun light penetration, thus reducing photosynthetic activity [2, 3]. As dyes are designed to resist breakdown with time, exposure to sunlight, soap and oxidizing agent cannot be easily removed by conventional wastewater treatment processes due to their complex structure and synthetic origins [4]. MB will cause increased heart rate, vomiting, shock, Heinz body formation, cyanosis, jaundice, quadriplegia and tissue necrosis in humans [5]. The commonly used methods for removing metal ions from waste water include precipitation, lime-coagulation, reduction, electrolytic removal, ion-exchange, reverse osmosis, membrane filtration, and solvent extraction[6-12]. A number of biosorbent have been used such as tree barks, saw dusts, activated rice husk, coconut shell, almond shell etc. for the adsorption of heavy metals. The objective of the present study is to investigate the possible use of activated carbon derived from *Cajanus Cajan pericarp* activated Carbon(CCPAC) as an alternative adsorbent material for removal of MB employing batch experiments.
Materials and Methods-All the chemicals used were of analytical or chemically pure grade. Distilled water was used throughout the investigation.

Preparation of activated carbon-*Cajanus cajan pericarp* was collected as an agricultural waste and washed several times with tap water followed by distilled water. The clean biomass so obtained was oven dried at 120^0C for 24hrs. The dry biomass was milled and sieved to get fine particles. The biomass was subjected to pyrolysis process using Muffle Furness. During slow carbonization of raw material in the absence of air at temperature range 700-800^0C, volatile product was removed and residue was converted into char. The char was then subjected

to chemical activation process using 25% zinc chloride solution. The adsorbent material obtained has been abbreviated as CCPAC.

Preparation of Methylene Blue solution -A stock solution of methylene blue of concentration 500 ppm (500 mg/L) was prepared by dissolving (0.5000)g of methylene blue in a 1000 mL volumetric flask, agitated by using a magnetic stirrer for a period of time and completed with distilled water up to the mark.

Characterization of CCPAC

FTIR analysis: FTIR of CCPAC is presented in Fig.1. The broad band at 3457.44 cm^{-1} indicates the presence of dissociated or associated –OH groups on the adsorbent surface. The band at 1637.05cm^{-1} represents N-H bending. The band at 1119.11$cm^{-1}$is indicative of CO stretching. The peak at 618.76cm^{-1}appears to be due to stretching vibration of carbon hydrogen bonding of alkyne linkages.

Scanning Electron Microscopy (SEM) Analysis: The surface morphology of activated carbon under investigation was examined using scanning electron microscopy. At x1000 magnification, SEM micrograph clearly revealed that wide varieties of pores are present in activated carbon along with fibrous structure. It is found that there are holes and caves type openings on the surface of the adsorbent which would have created more surface area available for adsorption.

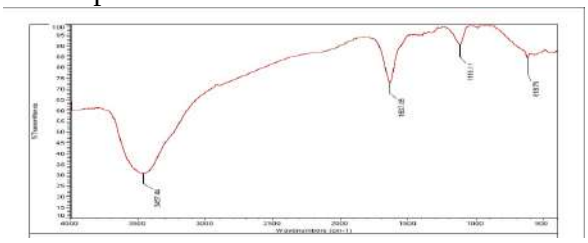


Fig1: FTIR of CCPAC

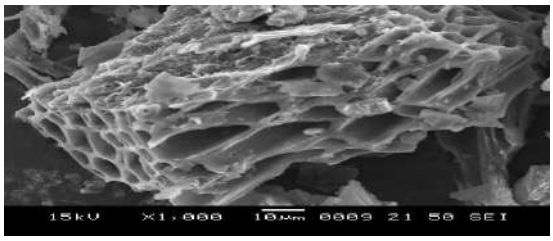


Fig 2: SEM of CCPAC

Results and discussion

Effect of pH-Effect of pH on the adsorption of MB using CCPAC as an adsorbent has been studied in the pH range 1to10. The relation between the pH of solution and percentage removal of MB has been shown in fig. 3. The most favorable adsorption was seen at basic pH 5–9 with 70 % removal of MG dye. So for further study pH 7–8 was maintained.

Effect of Contact time-Fig.4 represents the effect of contact time on removal of MB. The initial MB concentration taken was 30ppm. The percentage removal has found to increase with time from 35 to 76. After 100 minute negligible effect has been noticed on adsorption of MB. Thus 100 minute is the optimum time for these batch experiments.

Effect of adsorbent doses-The influence of CCPAC adsorbent doses was studied by varying it from 1 to 10 gm/lit for MB adsorption and the results are represented in Fig.5. The initial MB concentration taken was 30ppm.The percentage of MB removal was found to increase from 50 to 73. However after certain dose it becomes constant and it is treated as an optimum adsorbent dose, which is found to be 5gm/lit. for the CCPAC adsorbent.

Effect of Initial MB concentration-In the present study adsorption experiments were performed to study the effect of initial MB concentration by varying it from 10-100ppm solution is presented in Fig. 6. The results demonstrate that at a fixed adsorbent dose the percentage of MB removal decreases with increasing concentration of adsorbate.

Adsorption Isotherm-The isotherm data have been linearized using the Langmuir equation and is plotted between Ce/Qe versus Ce. The Langmuir constant q_m, which is measure of the monolayer adsorption capacity of CCPAC is obtained as 2.85. The Langmuir constant b which denotes adsorption energy, is found to be 0.315. The high value (0.9122) of regression correlation coefficient (R^2) indicates good agreement between the experimental values and isotherm parameters and also confirms the monolayer adsorption of MB onto the CCPAC. The dimensional parameter, R_L, which is a measure of

adsorption favorability is found to be 0.0194 ($0< R_L < 1$) which confirms the favorable adsorption process for MB on CCPAC adsorbent.

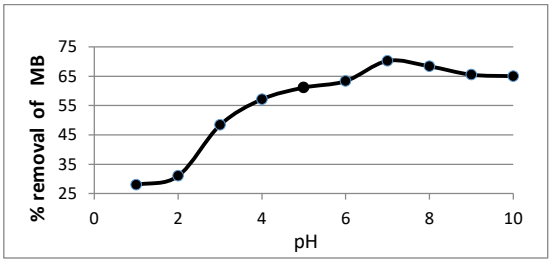


Fig.3: Effect of pH on adsorption of MB

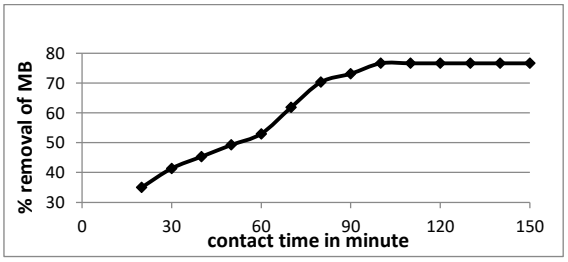


Fig.4: Effect of contact time on MB removal

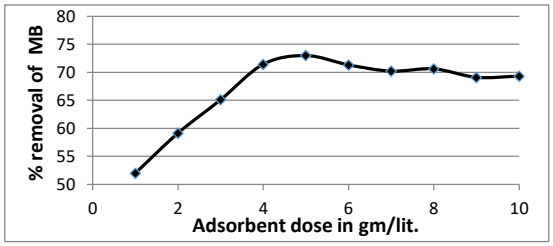


Fig. 5: Effect of adsorbent dose on MB adsorption

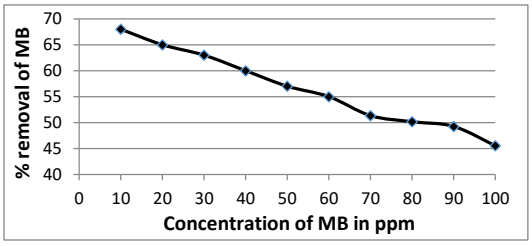


Fig 6: Effect of initial conc. of MB on adsorption

Conclusion-Utilization of waste material such as *Cajanus Cajan* pericarp for the removal of MB from the industrial waste-water is investigated. CCPAC is found to be better adsorbent for removal of MB. The maximum percentage for removal of MB is noticed at pH 7-8 with contact time 100 min. The percentage removal decrease with increase in initial MB concentration. At 5 gm/lit of optimum adsorption dose maximum removal efficacy has been noticed. The adsorption data are best fitted with Langmuir isotherm model which confirms the monolayer adsorption of MB onto CCPAC.

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30

Conductometric Studies of [CPHDD] and [CTMBCD] at Different Molar Concentrations and Different Percentage Compositions in Water-Ethanol Mixture

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Abstract

Conductivity play vital role in drug; diffusion, transmission, metabolisum (drug activity and drug effect) and exerition in pharmokinetics and pharmodynamics of drugs. Thermodynamic parameters affected by substituent's of drug. Considering these facts recently in this laboratory, conductometrically thermodynamic parameters of 4-[4-(4-chlorophenyl]-4-hydroxypiperidin-1-yl]-N,N-dimethyl-2,2-diphenylbutanamide [CPHDD] and (2S,6R)-7-chloro-2,4,6-trimethoxy-6'-methyl-3H,4'H-spiro[1-benzofuran-2,1'-]cyclo hex-2-ene]-3,4'-dione [CTMBCD] were investigated at different molar concentrations and different percentage compositions. This work mainly highlights on investigation of G, K and μ values. The thermodynamic parameters viz. ΔH, ΔS and ΔG for ion pair formation were determined from the value of ion association constant at 298K This technique is suitable and accurate to study pharmokinetics and pharmodynamics parameters.

Keywords: Conductometric measurements, thermodynamic parameters, [CPHDD], [CTMBCD] pharmokinetics and pharmodynamics.

Introduction:

Conductivity of drugs/ medicines play key role in medicinal chemistry. Conductometric measurements along with G, K and μ values, ΔH, ΔS and ΔG and biopharmaceutical parameters are responsible for the effective bioavailability of drug in vitro and in vivo correlations [1], which gives useful information regarding the permeability of drug in drug absorption and transmission of drug in pharmokinetics and pharmodynamics of drug in drug chemistry. Improvement of solubility and dissolution rate and oral bioavailability of poorly water soluble drugs are still the challenging aspects for the pharmaceutical technologists [2]. One of the safest methods of solubilisation is hydrotropic solubilisation [3] and by the addition of hydrotropic agents the aqueous solubilisation of insoluble drugs can be achieved. Many researchers highlighted the effect of the solubility enhancers (hydrotropic agents) [4, 5] and hence improved stability of the drug but no detailed explanation is available relating to the improvement phenomena.

Split of electrolyte conductivities into the ionic components ideally requires transference numbers, an accuracy to obtain exact readings for ground level laboratory for various parameters to chemist become difficult and important task and also serious experimental problems in many non-aqueous solvents for well equipped laboratories for pharmacokinetics and pharmacodynamics of drugs in drug chemistry. To overcome this problem conductance measurements provide very important and valuable information regarding ion-ion and ion-solvent interactions [6-7]. The conductometric studies of ionic association of divalent asymmetric electrolyte $Cu(NO_3)_2$ with Kryptofix-22 in mixed (MeOH-DMF) solvents at different temperatures were carried out by Gomaa and Al-Jahdalli [8].

Izonfuo and Obunwo [9] and Roy *et al* [10] studied the conductance of alkali metal in different mixtures mixed solvents. The thermodynamic parameters and Walden products of different complexes were studied by few researched and they also determined the comparison of transition metal complexes among the halide groups by [11]. Dubey [12] studied the interaction between sodium sulphate and 1-propanol, 1-butanol, 1-pentanol and 1-hexanol at different temperatures by conductometric technique [13]. The present investigation deals with the study of conductometric properties, thermodynamic behaviour and Walden product of 4-[4-(4-chlorophenyl]-4-hydroxypiperidin-1-yl]-N, N-dimethyl-2,2-diphenylbutanamide [CPHDD] and (2S, 6R)-7-chloro -2, 4, 6-trimethoxy-6'-methyl-3H, 4'H-spiro[1-benzofuran 2, 1'-] cyclohex-2-ene]-3,4'-dione[CTMBCD] in ethanol-water mixture at different concentrations and different percentage compositions at constant temperature i.e. 27^0C.

Experimental:

All the chemicals and solvents used for the synthesis were of A.R. grade. All the freshly prepared solutions were used for investigations. The solvents were purified by standard method [14]. Different concentration solutions of 0.1M 4-[4-(4-chlorophenyl]-4-hydroxypiperidin-1-yl]-N,N-dimethyl-2,2-diphenyl- butanamide [CPHDD] and (2S,6R)-7-chloro-2,4,6-trimethoxy-6'-methyl-3H,4'H-spiro[1-benzofuran-2,1'-]cyclohex-2-ene]-3,4'-dione[CTMBCD] were prepared. 0.1M solution of each drug was prepared and then by serial diluton method 0.075M, 0.050M and 0.025M were prepared in 100% water and ethanol-water mixture respectively. Similar solutions were prepared for 80% and 70% water-ethanol mixture. All the solutions of drug were always used a fresh in the present investigation.

In 50 ml glass beaker drug solution was taken and it was kept inside the thermostat for 15-20 minutes to attain the thermal equilibrium (27^0C). After achieving the thermal equilibrium, the conductivity was measured.

Results and Discussion:

During this investigation conductometric measurements of 100%, 80%, and 70% mixtures of water-ethanol were prepared. In first set 0.1M solution of **[CPHDD]** and in second set 0.1M solution of **[CTMBCD]** was prepared in conductivity water and by serial dilution method 0.075M, 0.050M and 0.025M solutions were prepared. At 27^0C the conductance of each solution was measured by conductivity bridge and result are cited in Table 1 and Table 2. From the data observed conductance (G), specific conductance (k) and molar conductance (μ) were determined by known literature method.

Table 1: Conductometric Measurements of [CPHDD] at different concentration

Determination of G, k and μ on different Concentrations at 27**°C**				
% of solution (**Water- ethanol**)	Concentration (M)	Observed conductance (G)	Specific conductance (k)	Molar conductance (μ)
100%	0.1 M	$0.60X10^{-3}$	0.5709606X10-3	5.709606
	0.075 M	$0.51\ X10^{-3}$	0.4853165X10-3	6.4708868
	0.050 M	$0.37\ X10^{-3}$	0.3520923X10-3	7.0418474
	0.025 M	$0.21\ X10^{-3}$	0.1998362X10-3	7.993448
80%	0.1 M	$0.73X10^{-3}$	0.6946687X10-3	6.9466873
	0.075 M	$0.70\ X10^{-3}$	0.6661207X10-3	8.8816093
	0.050 M	$0.61\ X10^{-3}$	0.5804766X10-3	11.609532
	0.025 M	$0.41\ X10^{-3}$	0.3901564X10-3	15.606256
70%	0.1 M	0.25 X10-3	0.2379002X10-3	2.3790025
	0.075 M	0.22 X10-3	0.2093522X10-3	2.7913629
	0.050 M	0.20 X10-3	0.1903202X10-3	3.806404
	0.025 M	0.14 X10-3	0.1332241X10-3	5.3289656

Table 2: Conductometric Measurements of [CTMBCD] at different concentration				
Determination of G, k and μ on different Concentrations at 27°**C**				
% of solution (**Water- ethanol**)	Concentration (M)	Observed conductance (G)	Specific conductance (k)	Molar conductance (μ)
100%	0.1 M	0.22X10-3	0.209352 X10-3	2.09352
	0.075 M	0.17 X10-3	0.161772 X10-3	2.15696
	0.050 M	0.12 X10-3	0.114192X10-3	2.28384
	0.025 M	0.08 X10-3	0.076128X10-3	3.04512
80%	0.1 M	0.16X10-3	0.152256X10-3	1.52256
	0.075 M	0.15 X10-3	0.14274X10-3	1.9032
	0.050 M	0.12 X10-3	0.114192X10-3	2.28384
	0.025 M	0.08 X10-3	0.076128X10-3	3.04512
70%	0.1 M	0.15 X10-3	0.14274X10-3	1.4274
	0.075 M	0.13 X10-3	0.123708X10-3	1.64944
	0.050 M	0.11 X10-3	0.104676X10-3	2.09352
	0.025 M	0.07 X10-3	0.066612X10-3	2.66448

From **Table-1 to Table-2**, it was observed that the observed conductance (G) and specific conductance (k) were decreases from [CPHDD] to [CTMBCD] continuously while molar conductance (μ) increases. Decrease in some conductance is due to number of phenolic-OH group present in the respective molecule. In [CPHDD] observed conductance continuously decreases from 0.1M concentration to 0.025M concentration continuously. This is due to the numbers of [CTMBCD] present in these solutions were continuously decreases. Same pattern was observed in percentage compositions of the mixture. Specific conductance of [CPHDD] decreases when the molar concentration and percentage composition of water decreases but the specific conductance increases at the same temperature. In [CPHDD] it was also observed that molar conductance increases from 0.1M concentration to 0.025M concentration as well as it increases in all percentage compositions. In 100% water molar conductance is highest while it will decreases from 100% to 70% water-ethanol percentage compositions. Molar conductance in 100% water is highest in all molar concentrations. Above results showed that [CPHDD] and [CTMBCD] are good drugs and will gave good pharmokinetics and pharmodynamics results of the standard drug. Same patterns of observed conductance, molar conductance and specific conductance were observed for [CTMBCD]. These results throw light on pharmokinetics of these two drugs. During this investigation it was observed that the molar conductance of [CPHDD] is more than [CTMBCD] which clearly indicates the drug effect of [CPHDD] is comparatively good than [CTMBCD]. It means that the absorption, transformation and metabolism of [CPHDD] is better than [CTMBCD], so [CPHDD] possesses best drug activity and drug effect than [CTMBCD].

The specific constant (Ksp), log (Ksp) and thermodynamics parameter viz. change in free energy (ΔG), change in entropy (ΔS) and change in enthalpy (ΔH) of [CPHDD] and [CTMBCD] were determined by known literature method at various molar concentration, percentage compositions and temperatures and result are cited in **Table 1** to **Table 8**.

Table 3 : Conductometric Measurements of [CPHDD] at different concentration						
Determination of Ksp, log Ksp, ΔG,ΔH and ΔS at different Concentrations at 27°C						
SYSTEM:DRUG CPHDD			**MEDIUM - 100% WATER**			
Temp (°C)	**Conc. (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
27	0.100	0.099790372	-1.000911358	5749.37757	-580158.4026	-1953.025934
	0.075	0.074842777	-1.125850107	6467.043561	-580158.4026	-1955.418154
	0.050	0.049895185	-1.301941363	7478.536846	-580158.4026	-1958.789798
	0.025	0.024947592	-1.602971367	9207.696116	-580158.4026	-1964.553662

Table 4 : Conductometric Measurements of [CPHDD] at different concentration						
Determination of Ksp, log Ksp, ΔG,ΔH and ΔS at different Concentrations at 27°C						
SYSTEM:DRUG [CPHDD]			**MEDIUM - 80% WATER**			
Temp (°C)	**Conc. (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
27	0.100	0.079832297	-1.097821375	6306.042527	-580158.4026	-1954.881484
	0.075	0.059874221	-1.222760124	7023.708518	-580158.4026	-1957.233704
	0.050	0.039916148	-1.398851376	8035.20178	-580158.4026	-1960.645348
	0.025	0.019958073	-1.699881393	9764.361124	-580158.4026	-1966.409212

Table 5 : Conductometric Measurements of [CPHDD] at different concentration						
Determination of Ksp, log Ksp, ΔG,ΔH and ΔS at different Concentrations at 27°C						
SYSTEM:DRUG [CPHDD]			**MEDIUM - 70% WATER**			
Temp (°C)	**Conc. (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
27	0.100	0.06985326	-1.155813321	6639.156535	-580158.4026	-1955.991864
	0.075	0.052389943	-1.280752074	7356.822548	-580158.4026	-1958.384084
	0.050	0.034926629	-1.456843323	8368.315793	-580158.4026	-1961.755728
	0.025	0.017463314	-1.757873327	10097.47506	-580158.4026	-1967.519592

Table 6: Conductometric Measurements of [CTMBCD] at different concentration						
Determination of Ksp, log Ksp, ΔG,ΔH and ΔS at different Concentrations at 27°C						
SYSTEM:DRUG [CTMBCD]			**MEDIUM - 100% WATER**			
Temp (°C)	**Conc. (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
27	0.100	3.925965087	0.593946433	-3411.713008	-580158.4026	-1922.488965
	0.075	2.944471816	0.469007696	-2694.047086	-580158.4026	-1924.881185
	0.050	1.962982544	0.292916437	-1682.553784	-580158.4026	-1928.252829
	0.025	0.981491271	-0.008113558	46.60543415	-580158.4026	-1934.016693

Table 7: Conductometric Measurements of [CTMBCD] at different concentration						
Determination of Ksp, log Ksp, ΔG,ΔH and ΔS at different Concentrations at 27**°C**						
SYSTEM:LIGAND [CTMBCD] **MEDIUM - 80% WATER**						
Temp (°C)	**Conc. (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
27	0.100	3.14077207	0.49703642	-2855.048074	-580158.4026	-1924.344515
	0.075	2.355579053	0.372097683	-2137.382152	-580158.4026	-1926.736735
	0.050	1.570386035	0.196006424	-1125.88885	-580158.4026	-1930.108379
	0.025	0.785193016	-0.105023571	603.2703682	-580158.4026	-1935.872243

Table 8 : Conductometric Measurements of [CTMBCD] at different concentration						
Determination of Ksp, log Ksp, ΔG,ΔH and ΔS at different Concentrations at 27**°C**						
SYSTEM:DRUG [CTMBCD] **MEDIUM - 70% WATER**						
Temp (°C)	**Conc. (M)**	**Ksp**	**Log Ksp**	**ΔG**	**ΔH**	**ΔS**
27	0.100	2.748175561	0.439044473	-2521.934061	-580158.4026	-1925.454895
	0.075	2.061131671	0.314105736	-1804.268139	-580158.4026	-1927.847115
	0.050	1.374087781	0.138014477	-792.7748368	-580158.4026	-1931.218759
	0.025	0.687043889	-0.687043889	936.3843814	-580158.4026	-1936.982623

From **Table-3** to **Table-8** it was observed for these drugs Ksp, log Ksp, ΔH and ΔS decreases continuously while ΔG increases when we go from 0.1M concentration solution to 0.025M concentration. Same pattern was observed in percentage composition of the mixture i.e. these thermodynamic parameters are highest in 100% water while least in 70% water-ethanol solvent. In [CTMBCD] the values of all thermodynamic parameter as well as Ksp and log Ksp are the greatest than [CPHDD].

Conclusion:

From this investigation it is clear that various functional groups such as electron donating, electron withdrawing, acidic, basic and various functional groups present in the molecule directly affect conductance, specific conductance, molar conductance, Ksp, ΔH, ΔS and ΔG values of that drug. The structure of the drug as well as nature of that drug directly affects these parameters. The temperature molar concentrations and percentage compositions are also responsible for changing the values of these parameters. The solute (drug)-solvent interactions, solvent-solvent interactions, solvent-solvent-solute interactions and solute-solute-solvent interactions are another factor which directly hamper these parameters. The internal geometry as well as internal and intra hydrogen bonding affect these parameters.

During this investigation it was also observed that the molar conductance of [CPHDD] is highest than [CTMBCD] which clearly indicates the drug effect of [CPHDD] is comparatively more than [CTMBCD].

Disclosure of conflict of interest:

Authors wish to state that there is no conflict of interest on this work.

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31

Synthesis and Characterization of Some Substituted Chalcone by the Green Synthesis Way (Grinding Method)

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ABSTRACT

The presented chalcone were synthesized by Claisen- Schmidt condensation of 2-hydroxy-3-nitro-5-methyl acetophenone (3) and o-chloro benzaldehyde. m-chloro and indol-3-carboxy aldehydes. All the synthesized compounds were characterized through NMR, IR, and elemental analysis. The synthetic methods used proved successful synthesis of the desired compound. Grinding technique is used to follow the green synthesis way for the synthesis of chalcone.

KEYWORDS*:* Chalcones, Green Synthesis (Grinding Technique), Claisen- Schmidt condensation.

INTRODUCTION

Alpha-beta unsaturated ketones or commonly referred as chalcones are one of the important classes of organic compounds frequently encountered in synthetic chemistry. They are important intermediates not only as key building blocks for the synthesis of core heterocycles such as pyrazole, isoxazole, triazole, flavone, benzodiazepine and pyrimidine in medicinal chemistry, but also as an invaluable chelating ligand for various lanthanide and transition metals in material chemistry. Chalcones, α, β-unsaturated carbonyls, play a crucial role in many biological processes as well as are well-known intermediates for synthesizing various heterocycles[1] and bear a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed[2]. Presence of enone functionality in chalcone shows the antibiotic activity.

Recent trends in organic synthesis utilize a non-conventional green technique such as ultrasound (sonochemistry), microwave irradiation, grinding and by using ionic liquids which have also been proved to have many advantages[3,4,5] Numerous solvents assisted and solvent-free methods have been reported for the preparation of pyrazoline derivatives. The present article elaborates on various green techniques reported previously for synthesis of chalcone derivatives, which will be useful for researchers for synthesizing chalcone derivatives in less time, yield effective and safely.

Green Synthesis of chalcone Derivatives "The design of chemical products and processes that are more environmentally benign and reduce negative impacts to human health and the environment"[6]. There are various green techniques available in the literature for synthesis of chalcone derivatives. Some green methods for organic synthesis of pyrazolines[7,8] Microwave Irradiation Ultrasonic Irradiation Grinding Technique Ionic Liquids Microwave Irradiation Microwave, which consists of electric and magnetic field, acts as a non-ionising reaction that causes ionic motions and rotations, but there is no change in molecular structure. At least one liquid polar is required in microwave synthesis[9]. Polar mechanism shows the

microwave effect that when polarity is increased from ground state towards the transition state during the reaction[10].

EXPERIMENTAL SECTION

The chalcones were synthesized by using 2-hydroxy-3-nitro-5-methyl acetophenone with some aldehydes (2-chloro Benzaldehyde, 3-chloro Benzaldehyde and Indol -3-carboxaldehyde) under alkaline condition. The chalcones were obtained yellow to brown and peach in colour and their synthesis were confirm by melting point method and from spectral interpretation. This is the general Claisen-Schmidt reaction[11] but I used the reaction by grinding was carried out in a mortar and pestle at room temperature. During the grinding, sudden change in colour took place, indicating the progress of reaction. The full conversion of the reaction mixture to a solid mass indicates the completion of reaction[12]

The chemicals and solvents used were of highest purity purchased commercially from Merck, S.D. Fine and Alfa Aesar Company Ltd. The melting points of all the synthesized compounds were recorded by Thiele's melting point apparatus as uncorrected values. The elemental analysis was carried out on Thermo Scientific CHNS elemental analyser. IR spectra were recorded on a Shimadzu instrument using KBr pallet. 1H NMR spectra were scanned by Brucker at 400 MHz using DMSO-d6 as solvent and TMS as an internal reference. 13C NMR spectrum of one sample (4a) was recorded on same instrument at 100 MHz. Experimental procedure for synthesis of 3-(substituted)-1-(2-hydroxy-5-methyl-3-Nitro phenyl) prop-2-en-1-ones 5(a-c).

SYNTHESIS OF CHALCONES

Preparation of p-methylphenyl acetate (1)

The p-cresol was refluxed along with acetic anhydride and anhydrous sodium acetate for an hour. The reaction mixture was cooled and poured into the ice-cold water containing crushed ice. Acetate layer was separated by means of separating funnel and several times washed with water. It was finally purified by distillation and the distillate fraction was collected at about 236^0C, to get the compound (1) b.p. 236^0C yield: 84.74%.

Preparation of 2-hydroxy-5-methyl acetophenone (2)

p-methyl phenyl acetate (1) was mixed with anhydrous $AlCl_3$ (1) and heated at 120^0C for 45minutes on an oil bath. The reaction mixture was decomposed in ice cold water containing 10% hydrochloric acid and allowing the solution to fall drop by drop into ice cold water with constant stirring. Green solid compound i. e crude ketone (2) was obtained, m.p. 47^0C, yield: 89%.

Preparation of 2-hydroxy-3-nitro-5-methyl acetophenone (3):

2-hydroxy-5-methyl acetophenone (2) was dissolved in acetic anhydride in a beaker and reaction mixture was kept in ice bath by maintain temperature below 5^0C. To this reaction mixture conc. HNO_3 was added dropwise with constant stirring till the solution becomes orange coloured and kept for 4-5 hrs. it was then decomposed with ice cold water. Yellow granules obtained were filtered and washed with water and then crystallized from ethanol, m.p. yield: 72%.

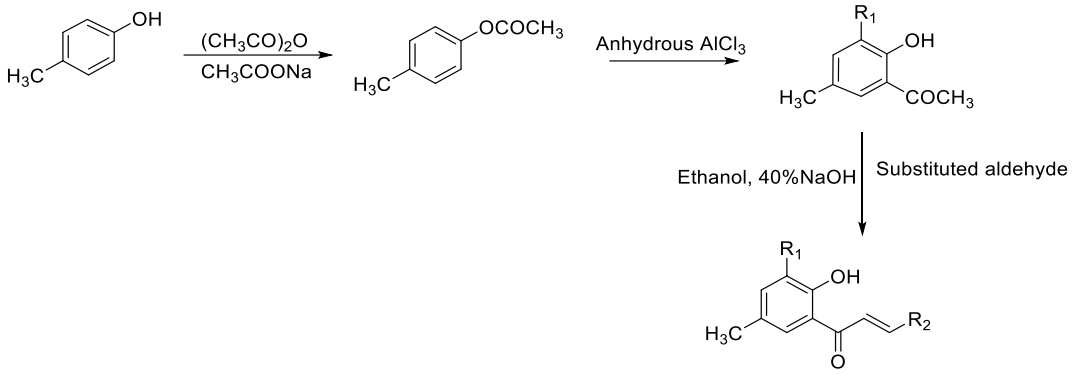
Preparation of β-unsaturated chalcones (4a–4c)

A mixture of 2-hydroxy-3-nitro-5-methyl acetophenone (3) (0.01mol) and chloro substituted aldehyde and indole 3-carboxyaldehyde, (0.01mol), aryl and ammonium bromide and

ammonium persulphate moist with few drops of water is ground at room temperature for 25 minutes in a mortar and pestle. The reaction mixture is allowed to stand for 25 min. Then Ice-cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The product was collected by vacuum filtration and then recrystallized from ethanol. The same procedure of grinding was applied by using anhydrous Barium hydroxide and then result of two procedure was compared. Name of the chalcone prepared are entitled below.

- 3-(2-chlorophenyl)-1-(2-hydroxy-5-methyl-3-nitrophenyl)prop-2-en-1-one (4a) M.P. 112^0C, yield: 74%.
- 3-(3-chlorophenyl)-1-(2-hydroxy-5-methyl-3-nitrophenyl)prop-2-en-1-one (4b) M.P 118^0C, yield: 84%.
- 1-(2-hydroxy-5-methyl-3-nitrophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (4c) M.P 154^0C, yield: 76%.

The complete experimental scheme for synthesis of above titled compounds is given below.



Scheme of 3-(substituted)-1-(2-hydroxy-5-methyl-3-Nitro phenyl) prop-2-en-1-ones 4(a-c). R_1= NO_2; R_2=2-Chloro benzaldehyde, 3- Chloro benzaldehyde, Indol-3-carboxyaldehyde,

RESULTS AND DISCUSSION

Spectroscopic Data: The IR, ^{1}H NMR and ^{13}C NMR spectral data showed expected signals or peaks which correspond to various groups present in each compound. Also, elemental analysis was found in full agreement with the proposed structures. The elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectral data of compounds 4(a-c) are shown below

3-(2-chlorophenyl)-1-(2-hydroxy-5-methyl-3-nitrophenyl)prop-2-en-1-one (4a)

Brown solid; M.P. 112^0C, yield: 74%.; Elemental Anal. Calcd. for $C_{16}H_{12}ClNO_4$.: C: 60.49, H: 3.81, O:4.41, Cl: 11.16 Found: C: 53.10, H: 2.40, O:3.98, Cl: 21.00. IR (KBr) cm-1: 3120 (Phenolic OH stretch), 2980 (Aromatic C-H stretch), 2850 (Aliphatic C-H stretch), 1695 (C=O stretch), 1520 (Aromatic C=C stretch),).1H NMR (400 MHz, DMSO-d6) δ (ppm): 1.51 (s, 3H, -CH3), 3.43 (s, 2H, -CH2), 3.80 (s, 1H, -OH), 8.15-8.32 (m, 6H, Ar-H).13C NMR (100MHz, DMSO-d6) δ (ppm): 40 (-CH2), , 195 (C=O), 123-136 (Ar-C), 149- 165 (C=C).

3-(3-chlorophenyl)-1-(2-hydroxy-5-methyl-3-nitrophenyl)prop-2-en-1-one (4b)

Dark brown solid; M.P 118^0C, yield: 84%.; Elemental Anal. Calcd. for $C_{16}H_{12}ClNO_4$.; C:53.10; H:2.40; N:3.98, Cl: 21.00. Found: C: 60.49; H: 3.81; N: 4.41, Cl:20.91. IR (KBr) cm-1: 3340 (Phenolic OH stretch), 2980 (Aromatic C-H stretch), 2910 (Aliphatic C-H stretch), 1615 (C=O stretch), 1515 (Aromatic C=C stretch), 1260 (C-O stretch).1H NMR (400MHz, DMSO-d6) δ (ppm): 1.51 (s, 3H, -CH3), 3.81 (s, 2H, -CH2), 5.13 (s, 1H, -OH), 6.99-7.90 (m, 6H, Ar-H).

1-(2-hydroxy-5-methyl-3-nitrophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (4c)

Peach color solid; M.P 154^{0}C, yield: 76%; Elemental Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.08; H: 4.38; N: 3.98, found C: 53.10; H: 3.40; N: 7.90. 1H NMR (400MHz, DMSO-d6) δ (ppm): 1.50 (s, 3H, -CH3), 3.38 (s, 2H, -CH), 4.10 (s, 1H, -OH), 6.77-7.65 (m, 6H, Ar-H).

CONCLUSION

In conclusion, a new series of 3-(substituted)-1-(2-hydroxy-5-methyl-3-Nitro phenyl) prop-2-en-1-ones i.e chalcones 4(a-c) bearing 4-methyl phenol i.e. p-cresol moiety were successfully synthesized in satisfactory yield by employing Claisen-Schmidt condensation of corresponding substituted 2-hydroxy-3-nitro-5-methyl acetophenone (3) and their structures were elucidated by chemical characteristics, elemental analysis and IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques.

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32

In-Silico Prediction of Phytoconstituents From Solanum Indicum for Antiepileptic Activity

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ABSTRACT

Objective

A persistent, non-communicable brain disorder is epilepsy. Its distinctive characteristic is recurrent seizures. One or more parts of the body may experience partial or generalised seizures, which are short bursts of uncontrollable movement that can occasionally be followed by loss of consciousness and control over bowel or bladder function. Compounds found in medicinal plants have been the source of many conventional medications. *In-silico* testing of *Solanum indicum* phytoconstituents for antiepileptic efficacy was a part of our investigation.

Methods

Utilizing Discovery studio, molecular docking is done to assess the pattern of interaction between the phytoconstituents from the *Solanum indicum* plant and the crystal structure of the epilepsy proteins (PDB ID: 6O4L). Later, SwissADME and pkCSM were used to screen for toxicity as well as the pharmacokinetic profile. **Results**

The docked results suggest that Solafuranone (-7.8 kcal/mol), Isofraxidin (-6.1 kcal/mol) for 6O4L macromolecule has best binding towards antiepileptic activity as compared to the standard (Acetazolamide) for 6O4L is -5.1 kcal/mol. Furthermore, pharmacokinetics and toxicity parameters were within acceptable limits according to ADMET studies.

Conclusion

Results from the binding potential of phytoconstituents aimed at antiepileptic activity were encouraging. It promotes the usage of *Solanum indicum* and offers crucial details on pharmaceutical research and clinical care.

1. INTRODUCTION

Solanum indicum, also known as Birhata, Badi Kateri, or Indian night shade, belongs to the Solanaceae family. It is a common upright undershrub in warmer parts of India, Asia, and Africa that grows up to 1.5 metres in height. Its height ranges from 0.30 to 1.8 metres. Nationally, 500–1000 MT are needed each year. The berries, leaves, roots, seeds, and stems of this plant have all been used in traditional medical systems to treat a wide range of ailments, including bronchitis, asthma, dry cough, rhinitis, dysuria, leucoderma, sexual dysfunction, insomnia, heart weakness, and pruritis.[1]

Solanum indicum, which is consumed as a vegetable in some regions of Africa, may prevent cardiovascular diseases. It was exciting to read the studies on how it may be used to treat hypertension. The extract's potent therapeutic and preventative benefits against hypertension may not have been possible without the presence

of chlorogenic acids. The antihypertensive effect might be due to other components. The findings urge further research into the extract as a possible treatment for hypertension.[2]

However, there are few studies on the phytoconstituents of *Solanum indicum* for the

antiepileptic activity. Thus, keeping the above information in view, the present investigation was designed to identify the potential phytochemicals of *Solanum indicum* against 6O4L using a molecular docking method.

2. MATERIALS AND METHODS

2.1. Platform for molecular docking

The computational docking study of all the phytoconstituents selected as ligands with antiepileptic activity as the target was performed using PyRx software.[3]

2.2. Protein preparation

The macromolecule is 6O4L, *in silico* analysis of selected phytoconstituents was performed on the 1.85 Å crystal structure of antiepileptic macromolecule with inhibitor, (PDB ID: 6O4L, having resolution Resolution: 1.85 Å, R-Value Free: 0.220, R-Value Work: 0.174, R-Value Observed: 0.176), which was retrieved from the protein data bank (https://www.rcsb.org). 6O4L is classified as Crystal Structure of ALDH7A1 mutant E399D complexed with NAD all other molecules, such as co-crystallized water molecules, unwanted chains, and nonstandard residues, were deleted. Using Discovery studio.[4]

2.3. Mechanism of Action

6O4L: Aldehyde dehydrogenase 7A1 (ALDH7A1) is an enzyme that catabolizes lysine, and some loss-of- function mutations in this gene result in pyridoxine-dependent epilepsy (PDE). To understand how the mutations affect NAD+ binding, the crystal structures of the mutant enzymes in complex with NAD+ were examined. At the tested dose of NAD+, these alterations result in less active tetrameric ALDH7A1.[5]

2.4. Ligand preparation

The three-dimensional (3D) structures of all constituents were retrieved using Avogadro software from the PubChem database available on the NCBI website (https://pubchem.ncbi.nlm.nih.gov/). However, the drawing of geometrical 2D structure was performed using the ChemSketch program. The two-dimensional (2D) structures were transformed into 3D models using the Avogadro software and the ligand structures were saved in the PDB format. All the chemical structures are shown in Figure 1.

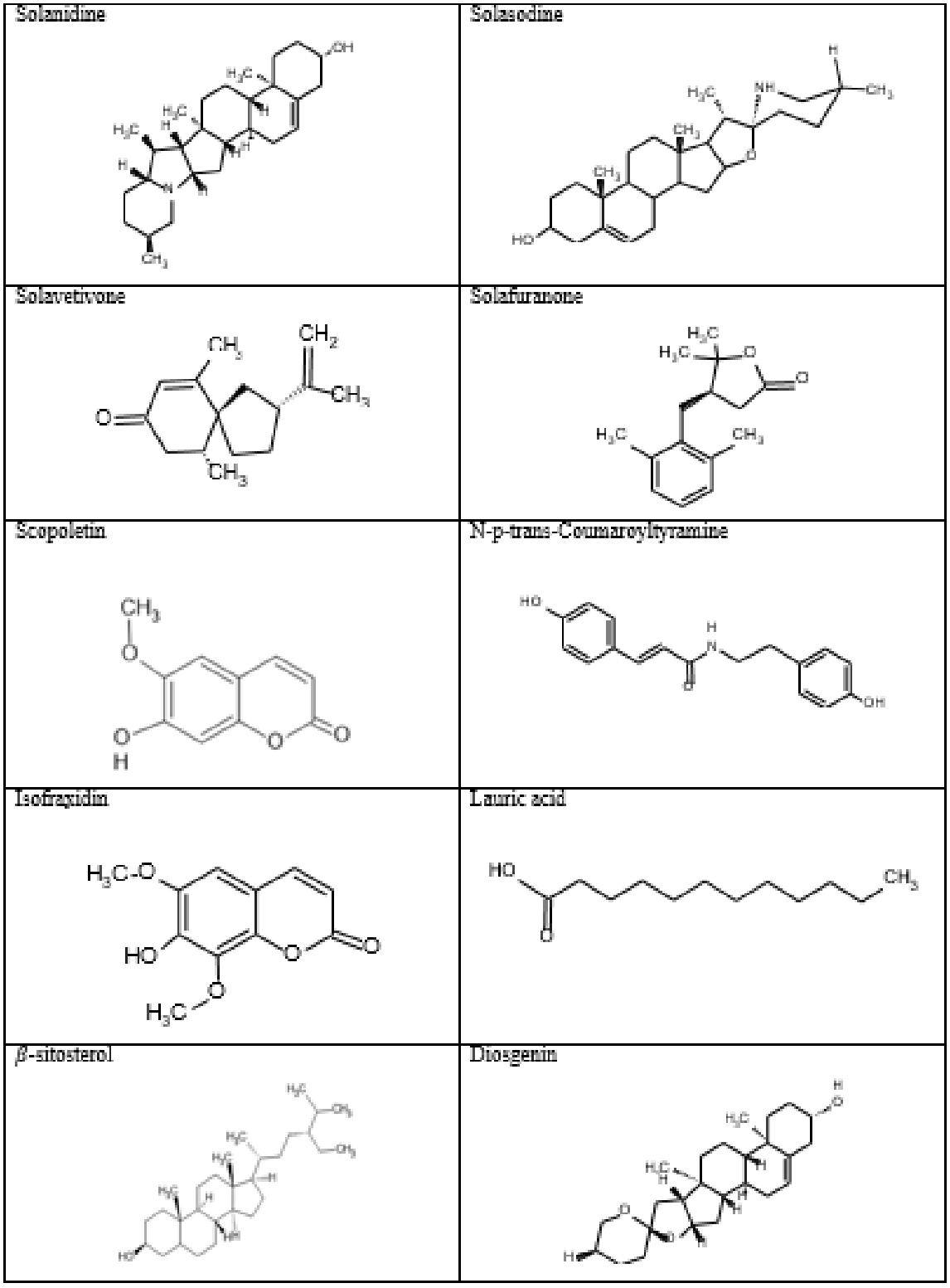


Fig. 1. Chemical structures of all selected phytoconstituents in the molecular docking studies

2.5. Standard Preparation

The standard is prepared steps such as, the 2D structure of standard drug was made using chem sketch program, then the 2D structure was converted into 3D model using Avogadro Software, it was saved in PDB format.
By using PyRx molecular docking of Acetazolamide was done with 6O4L.

2.6. Molecular docking

Molecular docking evaluates the protein-ligand interactions and estimates the scoring function based on the geometry to predict the binding affinity of the ligand molecule[6,7]. We applied molecular docking studies to investigate the binding pattern of selected phytoconstituents (Figure 1) and the standard drug, along with the crystal structure of antiepileptic activity macromolecule (PDB ID: 6O4L). The molecular docking study was performed using PyRx software, Binding affinity was explored using the Vina wizard tool. The final results were analysed and visualized using Discovery Studio 2020 Client [8], with bound ligands as the standard. Visualization of protein ligand interaction reflects the number of interactions and active residues responsible for significant binding at the active site of the target enzyme.

2.7. Absorption, distribution, metabolism, and excretion (ADME) and toxicity prediction

The selected phytoconstituents and standard drug were further checked for drug-likeness properties according to Lipinski's rule. During drug development, it is necessary to predict the tolerability of phytochemicals before being ingested by humans and animal models. The pharmacokinetic profile (ADME) and toxicity predictions of ligands were conducted using SwissADME (http://www.swissadme.ch) and pkCSM (an online server database predicting small-molecule pharmacokinetic properties using graph-based signatures, (http://biosig.unimelb.edu.au/pkcsm/prediction). To analyse the toxicological properties of ligands, Simplified Molecular Input Line Entry System (SMILES) notations or PDB files were uploaded, followed by selecting the required models for generating numerous information about structure-related effects[9,10].

3. RESULT AND DISCUSSION

The present study aimed to explore the inhibitory potential of the phytoconstituents present in *Solanum indicum* targeting antiepileptic activity. In this study, we performed molecular docking studies of all phytoconstituents found in *Solanum indicum* using AutoDock Vina, followed by a study of interacting amino acid residues and their influence on the inhibitory potentials of the active constituents. Selected phytoconstituents showing the best fit were further evaluated for absorption, distribution, metabolism, excretion, and toxicological (ADMET) properties using SwissADME and pkCSM servers.

3.1 Molecular docking

The docking scores and binding energies of all chemical constituents of *Solanum indicum* targeting antiepileptic activity (PDB ID: 6O4L) and binding interactions with amino acid residues are presented in Table 1 respectively.

Table 1. Binding interaction of ligands from *Solanum indicum* targeting antiepileptic activity (PDB ID:6O4L)

Sr. No.	Chemical constituent	PubChem ID	Docking Score
			6O4L
1.	Solanidine	65727	-10.0

2.	Solasodine	5250	-9.0
3.	Solavetivone	442399	-7.3
4.	Solafuranone	11107208	-7.8
5.	Scopoletin	5280460	-6.5
6.	N-p-trans-Coumaroyltyramine	5372945	-6.7
7.	Isofraxidin	5318565	-6.1
8.	Lauric acid	3893	-3.7
9.	β-sitosterol	222284	-7.1
10.	Diosgenin	99474	-8.1
Standard Drug			
11	Acetazolamide	1986	-5.1

The binding affinities of phytoconstituents ranged from –10.0 to -3.7 kcal/mol. From the docked results, it is evident that the compounds, Solanidine exhibit the most favourable binding affinity (−10.0 kcal/mol) in complex with selected macromolecules (PDB ID: 6O4L) as compared to other docked compounds i.e., Solsodine (-9.0 kcal/mol), Diosgenin (-8.1 kcal/mol), Solafuranone (−7.8. kcal/mol), Solavetivone (−7.3 kcal/mol), Beta sitosterol (-7.1 kcal/mol), N-p-trans-Coumaroyltyramine (−6.7 kcal/mol), Scopoletin (−6.5 kcal/mol), Isofraxidin (−6.1 kcal/mol), Lauric acid (−3.7 kcal/mol). Visual examination of the computationally docked optimal binding poses of phytoconstituents on selected macromolecules (i.e., 6O4L) revealed the significant involvement of various types of interactions, such as hydrogen bonding and hydrophobic interactions, including π–π stacking and π–alkyl and alkyl interactions, in the stability of the binding of the phytoconstituents to 6O4L.

The binding affinity of the standard (Acetazolamide) for 6O4L is -5.1 kcal/mol.

3.1.1. Solafuranone, 6O4L

The number of intermolecular hydrogen bonds, the binding energy of ligand 6O4L stable complexes, and the number of nearest amino acid residues were also determined for selected compound Solafuranone All synthesized derivatives formed complexes with target proteins. Analysis of interactions of the 6O4L protein complex and ligand Solafuranone showed that the ligand molecule is oriented due to Conventional Hydrogen

bond with THR A: 346 amino acid residue and Pi-Pi Stacked interaction with PHE A: 401 amino acid residue were found.

3.1.2. Isofraxidin, 6O4L

An analysis of the interactions between the 6O4L protein complex and the Isofraxidin ligand was also carried out, which showed that the ligand molecule is oriented due to conventional hydrogen bond with the ASP A: 399, THR A: 346, PHE A: 401 amino acid residue and Pi-Alkyl interaction with ALA A: 349 amino acid residue were found.

3.1.3. Acetazolamide, 6O4L

The binding affinity of the standard (Acetazolamide) for 6O4L is -5.1 kcal/mol. the

interactions between the 6O4L protein complex and the Acetazolamide ligand was also carried out, which showed that the ligand molecule is oriented due to conventional hydrogen bond with the PHE A:166, THR A:164 amino acid residue, Carbon hydrogen bond with PRO A:193 amino acid residue, Pi-Sulfur interaction with PHE A:166 amino acid residue, Pi-Cation interaction with LYS A:190 and Pi-Alkyl interaction with ALA A:165, ALA A:192 amino acid residue were found.

Table No. 2. Interactions with amino acid residue.

Sr. No.	Molecule	Binding Energy (kcal/mol)	H bond	Main amino acid interactions	
				Pi-alkyl, alkyl, Pi-S/Pi-Pi, T shaped/halogen/unfavourable donor-donor interactions	Van der Waals interactions
1	Solanidine	-10.0	No interactions	ALA A:192, ALA A: 165, VAL A: 250	No interactions
2	Solasodine	-9.0	GLY A: 226	VAL A: 250, PRO A: 193	No interactions
3	Solavetivone	-7.3	ASN A: 379, ASN A: 46	TYR A: 41	No interactions
4	Solafuranone	-7.8	THR A: 346	PHE A: 401	No interactions
5	Scopoletin	-6.5	THR A: 164, PHE A: 401	CYS A: 302, ALA A: 165	No interactions
6	N-p-trans-Coumaroyltyramine	-6.7	SER A: 460	PHE A: 168, CYS A: 302, TRP A: 175, PHE A: 468	No interactions
7	Isofraxidin	-6.1	ASP A: 399, PHE	ALA A: 349	No interactions
8	Lauric acid	-3.7	PHE A: 292	PRO A: 288, LEU A: 285, PRO A: 458	No interactions
9	β-sitosterol	-7.1	No interactions	TRP A: 31, ALA A: 207, LYS A: 204, LYS A: 208, VAL A: 209, ALA A: 92	No interactions
10	Diosgenin	-8.1	ASN A: 379	TYR A: 41, PHE A: 166	No interactions
11	Acetazolamide	-5.1	THR A: 164, PHE A: 166, PRO A: 193	ALA A: 165, ALA A: 192, LYS A: 190	No interactions

3.2. ADMET study

Pharmacokinetic profile (ADME) and toxicity predictions of the ligands are important attentive parameters during the transformation of a molecule into a potent drug. In the present study, these parameters were assessed using SwissADME and pkCSM. The absorption potential and lipophilicity are characterized by the partition coefficient (Log *P*) and topological polar surface area (TPSA), respectively. For better penetration of a drug

molecule into a cell membrane, the TPSA should be less than 140 Å. However, the value of Log *P* differs based on the drug target. The ideal Log *P* value for various drugs are as follows: oral and intestinal absorption,
1.35 − 1.80; sublingual absorption, > 5; and central nervous system (CNS)[11]. The aqueous solubility of ligands ideally ranges from − 6.5 to 0.5 [12], while the blood brain barrier (BBB) value ranges between − 3.0 and 1.2 [13]. In addition, non-substrate P-glycoprotein causes drug resistance [14].
In our study, all the selected ligands followed the TPSA parameter, P-glycoprotein non-inhibition, thereby showing good intestinal absorption and an acceptable range of BBB values. All the compounds showed aqueous solubility values within the range. Further, it was predicted that the selected ligands do not show AMES toxicity, hepatotoxicity, and skin sensitivity. In addition, it did not inhibit hERG-I (low risk of cardiac toxicity). Lipinski's rule violations, *T. pyriformis* toxicity, minnow toxicity, maximum tolerated dose, rat acute oral toxicity, and chronic toxicity are depicted in table.

Table 3. ADME and toxicity predicted profile of ligands with superior docking score

ADMET Properties	Formula	MW (g/mol)	Log P	PSA (Å^2)	HB donor	Hb acceptor	Aqueous solubility (Log mol/L)	Human intestinal absorption (%)	Blood Brain Barrier
Solanidine	$C_{27}H_{43}NO$	397.647	5.655	23.47 Å^2	1	2	-4.927	92.975	0.695
Solasodine	$C_7H_{43}NO_2$	413.64	5.2869	41.49 Å^2	2	3	-3.809	92.324	0.035
Solavetivone	$C_{15}H_{22}O$	218.33	3.9042	17.07 Å^2	0	1	-4.615	95.873	0.635
Solafuranone	$C_{15}H_{20}O_2$	232.323	3.18764	26.30 Å^2	0	2	-3.551	95.523	0.206
Scopoletin	$C_{10}H_8O_4$	192.17	1.5072	59.67 Å^2	1	4	-2.504	95.277	-0.299
N-p-trans-Coumaroyltyramine	$C_{17}H_{17}NO_3$	283.327	2.4699	69.56 Å^2	3	3	-3.165	90.031	-0.552
Isofraxidin	$C_{11}H_{10}O_5$	222.196	1.5158	68.90 Å^2	1	5	-2.458	95.588	-0.377
Lauric acid	$C_{12}H_{24}O_2$	200.322	3.9919	37.30 Å^2	1	1	-4.181	93.379	0.057
β-sitosterol	$C_{29}H_{50}O$	414.718	8.0248	20.23 Å^2	1	1	-6.773	94.464	0.781
Diosgenin	$C_{27}H_{42}O_3$	414.63	5.7139	38.69 Å^2	1	3	-5.713	96.565	0.2
Acetazolamide	$C_4H_6N_4O_3S_2$	222.251	-0.8561	151.66 Å^2	2	6	-2.428	59.043	-0.622

Table 3 Continued

ADMET Properties	P-glyco-protein substrate	Total clearance [Log mL/(min.kg)]	Bioavailability score score	AMES toxicity	Max tolerated dose [Log mg/(kg.d)]	hERG I inhibitor	hERG II inhibitor
Solanidine	YES	0.028	0.55	NO	-0.882	NO	YES

Solasodine	YES	0.09	0.55	NO	-0.375	NO	YES
Solavetivone	NO	1.225	0.55	NO	0.044	NO	NO
Solafuranone	NO	1.256	0.55	NO	0.526	NO	NO
Scopoletin	NO	0.73	0.55	NO	0.614	NO	NO
N-p-trans-Coumaroyltyramie	YES	0.265	0.55	NO	-0.213	NO	YES
Isofraxidin	NO	0.713	0.55	NO	0.56	NO	NO
Lauric acid	NO	1.623	0.85	NO	-0.34	NO	NO
β-sitosterol	NO	0.628	0.55	NO	-0.621	NO	YES
Diosgenin	NO	0.328	0.55	NO	-0.559	NO	YES
Acetazolamide	NO	-0.01	0.55	NO	1.263	NO	NO

Table 3 Continued

ADMET Properties	**Acute oral rat toxicity. LD50(mol/kg)**	**Oral rat chronic toxicity (Log mg/kgbw/day)**	**Hepatotoxicity**	**Skin sensation**	**T.Pyriformis toxicity (Log µg/L)**	**Minnow toxicity (Log mmol/L)**	**Lipinski's rule Violation**
Solanidine	2.596	1.334	YES	NO	0.378	-0.493	YES (1)
Solasodine	2.489	1.332	YES	NO	0.311	0.381	YES (1)
Solavetivone	1.643	1.19	NO	YES	1.453	0.874	YES (0)
Solafuranone	1.865	1.947	NO	YES	2.151	0.557	YES (0)
Scopoletin	1.95	1.378	NO	NO	0.516	1.614	YES (0)
N-p-trans-Coumaroyltyramine	2.17	1.271	NO	NO	1.008	1.514	YES (0)
Isofraxidin	2.326	1.825	NO	NO	0.431	1.862	YES (0)
Lauric acid	1.511	2.89	NO	YES	0.954	-0.084	YES (0)
β-sitosterol	2.552	0.855	NO	NO	0.43	-1.802	YES (1)
Diosgenin	1.921	1.452	NO	NO	0.399	0.247	YES (1)
Acetazolamide	2.292	2.143	NO	NO	0.239	2.895	YES (0)

3.3. Interaction of Standard Drug (Acetazolamide) with 6O4L

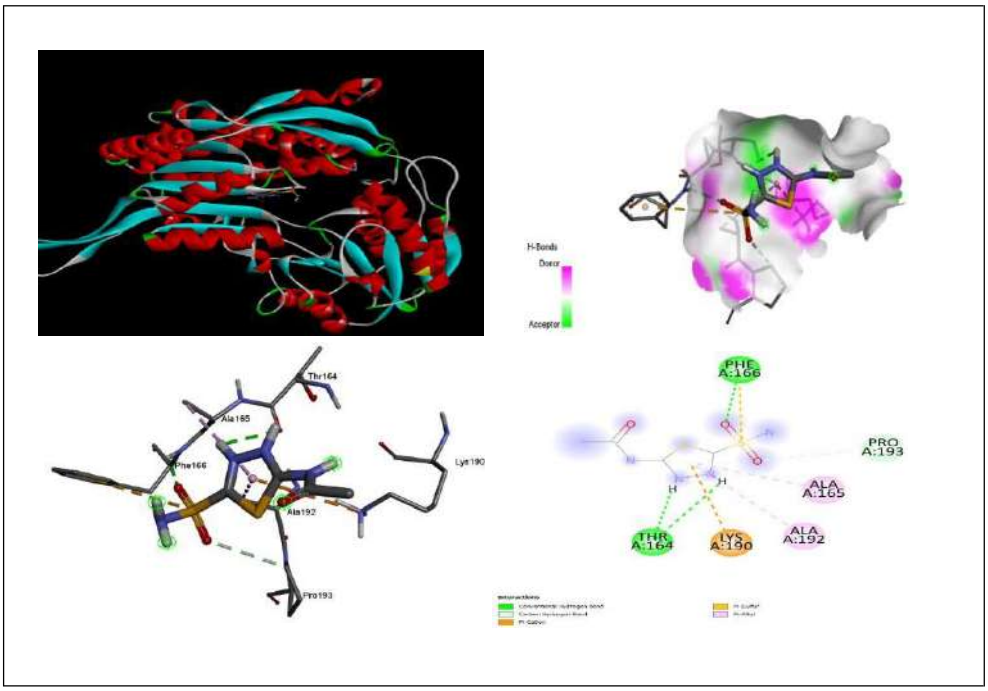
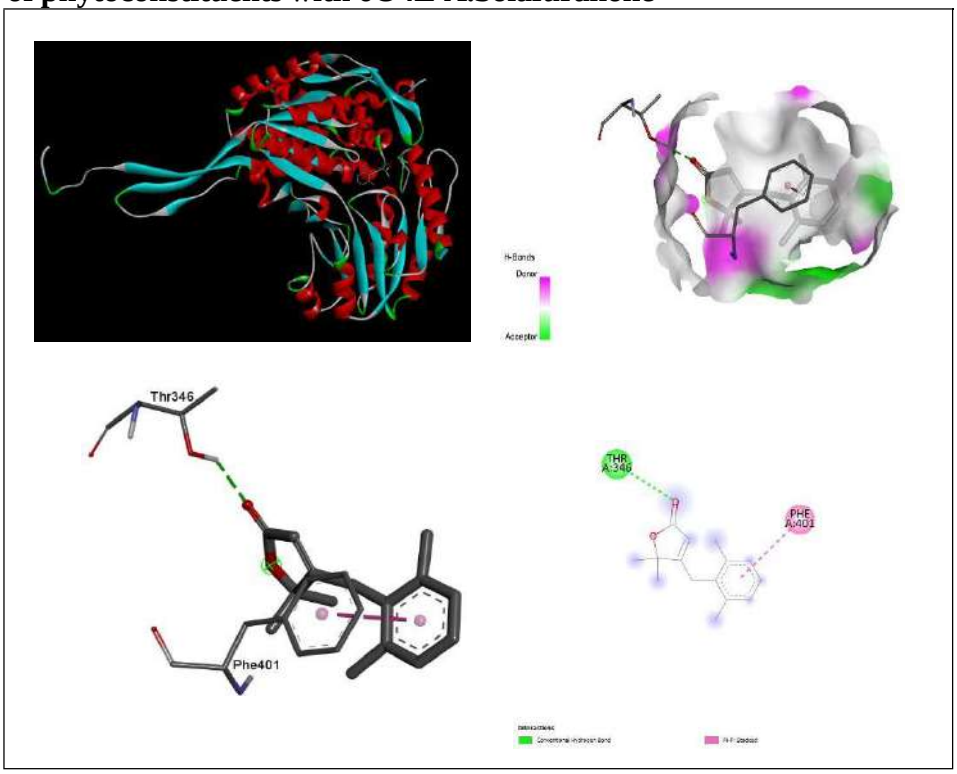


Fig. 2. Docking scores and binding interaction of Acetazolamide (PDB ID: 6O4L). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

3.4. Interactions of phytoconstituents with 6O4L A.Solafuranone



B.Isofraxidin

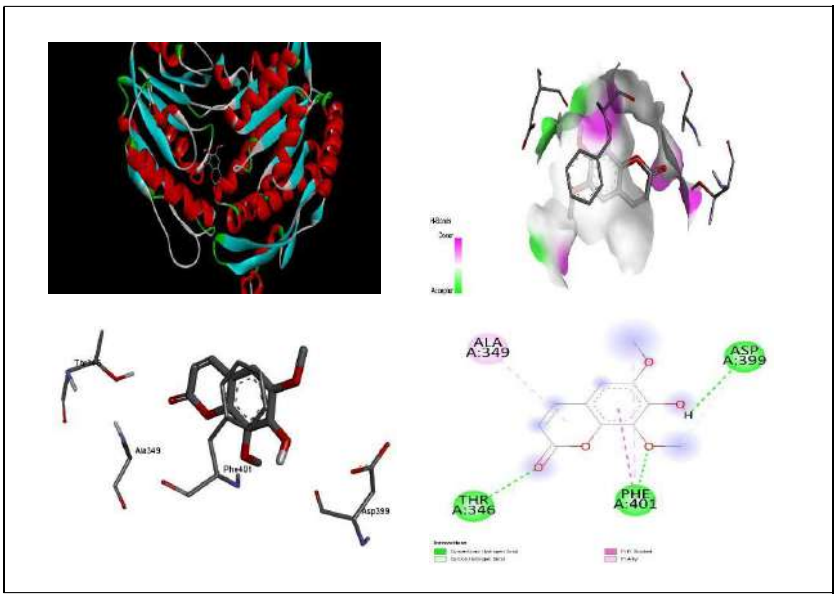


Fig. 3. Docking scores and binding interaction of phytoconstituents (PDB ID: 6O4L). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

3.5. Boiled Egg



Fig no. 4. Combined Boiled Egg Diagram

Table no. 4. Name of molecules contained in Boiled Egg Diagram

MOLECULE NUMBER	MOLECULE NAME
1	Solanidine
2	Solasodine
3	Solavetivone
4	Solafuranone
5	Scopoletin
6	N-p-trans-Coumaroyltyramine
7	Isofraxidin
8	Lauric acid
9	β-sitosterol
10	Diosgenin
11	Acetazolammide

BOILED means **B**rain **O**r **I**ntestina**L** **E**stimate**D** permeation predictive model. The boiled egg diagram shows two regions white region and yellow region.

The white region is the physicochemical space of molecules with highest probability of being absorbed by the gastrointestinal tract, and the yellow region (yolk) is the physicochemical space of molecules with highest probability to permeate to the brain.
In addition, the points are coloured in blue if predicted as actively effluxed by P-gp (PGP+) and in red if predicted as non-substrate of P-gp (PGP-).

4. CONCLUSION

In this study, we have carried out an *in-silico* screening of the phytoconstituents of *Solanum indicum* plant. This study demonstrated the sixteen compounds from *Solanum indicum* plant, (Solanidine, Solasodine, Solavetivone, Solafuranone, Scopoletin, N-p-trans-Coumaroyltyramine, Isofraxidin, Lauric acid, β-sitosterol, Diosgenin). The selected phytocompounds showed docking scores ranging from –10.0 to −3.7 kcal/mol in 6O4L. Among all, Solafuranone and Isofraxidin gave the highest binding energy (−7.8 kcal/mol) and (−6.1 kcal/mol) in complex with 6O4L, whereas the reference compound, Acetazolamide showed a docking score with a binding energy of -5.1 kcal/mol. Furthermore, these ligands exhibited good ADMET properties. To summarize, phytoconstituents present in *Solanum indicum* possess strong effects against 6O4L and could be further evaluated for their antiepileptic effect, as well as for the development of alternative drugs with fewer side effects for the treatment of epilepsy.

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33

Deep Discoveries in Chemistry: Unraveling the Mysteries at the Molecular Level

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Abstract:

This research article delves into the profound discoveries and advancements in the field of chemistry, exploring breakthroughs that have unraveled the mysteries at the molecular level. From the elucidation of complex chemical reactions to the design of novel materials with unprecedented properties, these deep discoveries have significantly impacted various scientific disciplines and technological applications. This article provides an overview of key developments, showcasing the depth and breadth of contemporary research in chemistry.

Key Words: Chemistry Discoveries, Molecular-Level Understanding, Sustainable Practices, Environmental Chemistry, Bottom-Up Nanofabrication etc.

Introduction:

Deep discoveries in science, especially those at the molecular level in fields such as chemistry, play a crucial role in advancing scientific knowledge and driving technological innovation. Deep discoveries provide a fundamental understanding of the underlying principles governing natural phenomena. This knowledge serves as the basis for developing theories and frameworks that explain complex processes at a molecular level[1]. Scientific breakthroughs often translate into technological innovations. Discoveries at the molecular level can lead to the development of new materials, processes, and technologies with applications ranging from medicine and electronics to energy and environmental management. Deep discoveries stimulate curiosity[2] and open up new avenues for research. Discoveries in molecular biology and pharmacology contribute to the development of new drugs and therapies.

Deep discoveries in chemistry contribute to the development of green and sustainable practices. Advances at the molecular level often contribute to the convergence of technologies[3]. For example, discoveries in nanotechnology, which deals with materials at the nanoscale, have implications not only in material science but also in medicine, electronics, and energy storage. Deep discoveries have the potential to revolutionize entire industries. For example, advancements in molecular electronics may lead to the development of smaller, faster, and more efficient electronic devices, transforming the semiconductor industry. In summary, deep discoveries in science, particularly at the molecular level, are instrumental in shaping the scientific landscape and driving technological progress. They provide the foundation for innovations that have far-reaching implications across diverse fields, contributing to the betterment of society and the advancement of human knowledge.

Objectives and Materials and Methods:

Several discoveries in the field of chemistry have challenged traditional understanding, leading to paradigm shifts and opening new avenues for synthesis. Here are a few notable examples:

1. Molecular Machines and Nanotechnology: The development of molecular machines, such as synthetic molecular motors and switches, challenges traditional notions of static molecular

structures. Researchers have created nanoscale machines capable of controlled movement, enabling potential applications in drug delivery, nanoelectronics, and other fields.

2. Metathesis Reaction: The discovery of metathesis reactions, particularly the development of olefin metathesis by Grubbs[4], Schrock, and Chauvin, challenged traditional thinking about the limitations of organic synthesis. This groundbreaking discovery provided a powerful tool for creating carbon-carbon double bonds in a controlled manner, revolutionizing the synthesis of complex organic molecules.

3. Click Chemistry: Click chemistry, introduced by K. Barry Sharpless and others, represents a set of highly efficient and selective reactions that challenge traditional synthesis methods. These reactions, characterized by their reliability and simplicity, have found widespread use in various applications, including drug discovery and materials science[5].

4. Molecular Electronics: The field of molecular electronics challenges traditional semiconductor technology by exploring the use of individual molecules as electronic components. Researchers aim to create electronic devices at the molecular scale, potentially leading to smaller, faster, and more energy-efficient electronics.

5. Green Chemistry Principles: The emergence of green chemistry[6] challenged traditional chemical practices by emphasizing the importance of designing environmentally friendly processes. This approach considers the environmental impact at every stage of chemical production, leading to the development of more sustainable and less toxic chemical syntheses.

6. C–H Activation: Traditional organic synthesis often involves functionalizing carbon-hydrogen (C–H) bonds, which were once considered unreactive. Recent advancements in C–H activation chemistry challenge this convention, allowing chemists to directly functionalize C–H bonds, streamlining synthetic routes and reducing the number of steps required for complex molecule synthesis.

7. Supramolecular Chemistry: Supramolecular chemistry challenges traditional views by focusing on non-covalent interactions to create complex, hierarchical structures. The field explores the assembly of molecules into larger, functional structures, leading to applications in materials science, drug delivery[7], and catalysis.

8. Chemoselective Reactions: Discoveries in chemoselective reactions challenge traditional chemical methods by enabling the selective modification of one functional group in the presence of others. This has profound implications in the synthesis of complex molecules, where multiple functional groups may be present.

9. Metal-Organic Frameworks (MOFs): The development of metal-organic frameworks[8] challenges traditional notions of solid-state chemistry. MOFs are porous materials with high surface areas, and their design and synthesis have opened up new possibilities for gas storage, catalysis, and separation processes.

10. Directed Evolution of Enzymes: The directed evolution of enzymes challenges the traditional concept that enzymes have fixed structures and functions. Through directed evolution, researchers can engineer enzymes with enhanced or entirely new functionalities, leading to applications in pharmaceuticals, biofuels, and more.

These examples illustrate how breakthrough discoveries in chemistry have questioned established norms, prompting researchers to explore novel avenues for synthesis and innovation. These paradigm shifts contribute to the continuous evolution and advancement of the field.

Conclusion:

From the above points of informative aspects, deep discoveries represent a journey into the unknown, reshaping our understanding of the molecular world and propelling technological advancements. They underscore the dynamic nature of science, where each revelation not only expands our knowledge but also sparks innovation that has far-reaching consequences for society. As we continue to unravel the mysteries at the molecular level, the transformative impact on both scientific understanding and technological applications will undoubtedly persist, driving the evolution of science and technology.

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34

Synthesis, Characterization of (3-Chloro-benzylidene) – (4-Phenyl-thiazol-2-yl) amine and Studied their antioxidant Activity

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Abstract -

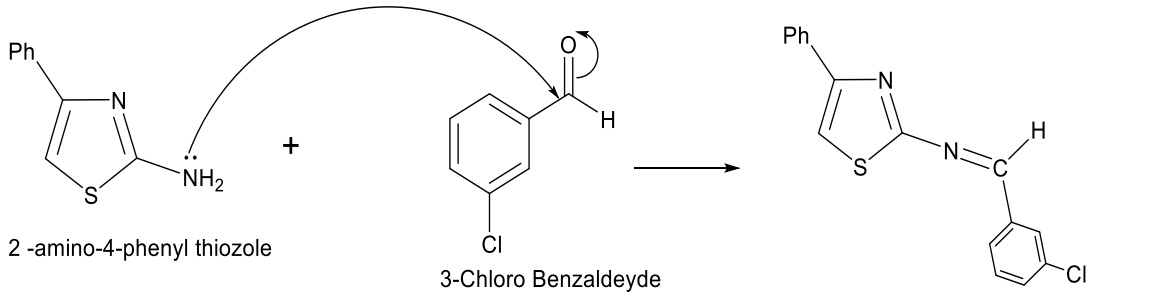
In the current study, substituted aromatic aldehydes (2a-c) were combined with 2- amino-4-phenyl thiazole to create a series of 4-phenyl-thiazolyl substituted Schiff bases (3a-c) derivatives. The IR and 1H-NMR of all the produced compounds validated their structures and its antibacterial activity was examined. All the title compounds were screened for their antibacterial activity. Most of the compounds exhibited moderate antimicrobial activity.

Keywords: Schiff's base; Aromatic Aldehydes; 3-Chloro-benzylidene) – (4-Phenyl-thiazol-2-yl) amine, Potassium ferricyanide.

Introduction-

In pharmaceutical chemistry, thiazole derivatives have been extremely important. Thiazole have a wide variety of pharmacological properties, including antimicrobial[1-4], analgesic[6-7], anticonvulsant[8-9], and antioxidant[10], hypolipidemic[11], anti HIV-1 [12-13], adenosine receptor antagonist[14-15] and osteoporosis inhibitor[16]. For the creation of antimalarial drugs, Schiff bases have proven to be intriguing moieties[17–18]. As potential antibacterial agents, Schiff bases have been mentioned[19–21]. It is imperative to find and create more powerful antifungal medicines, and several Schiff bases are well-known to be effective ones[22].

Reaction scheme

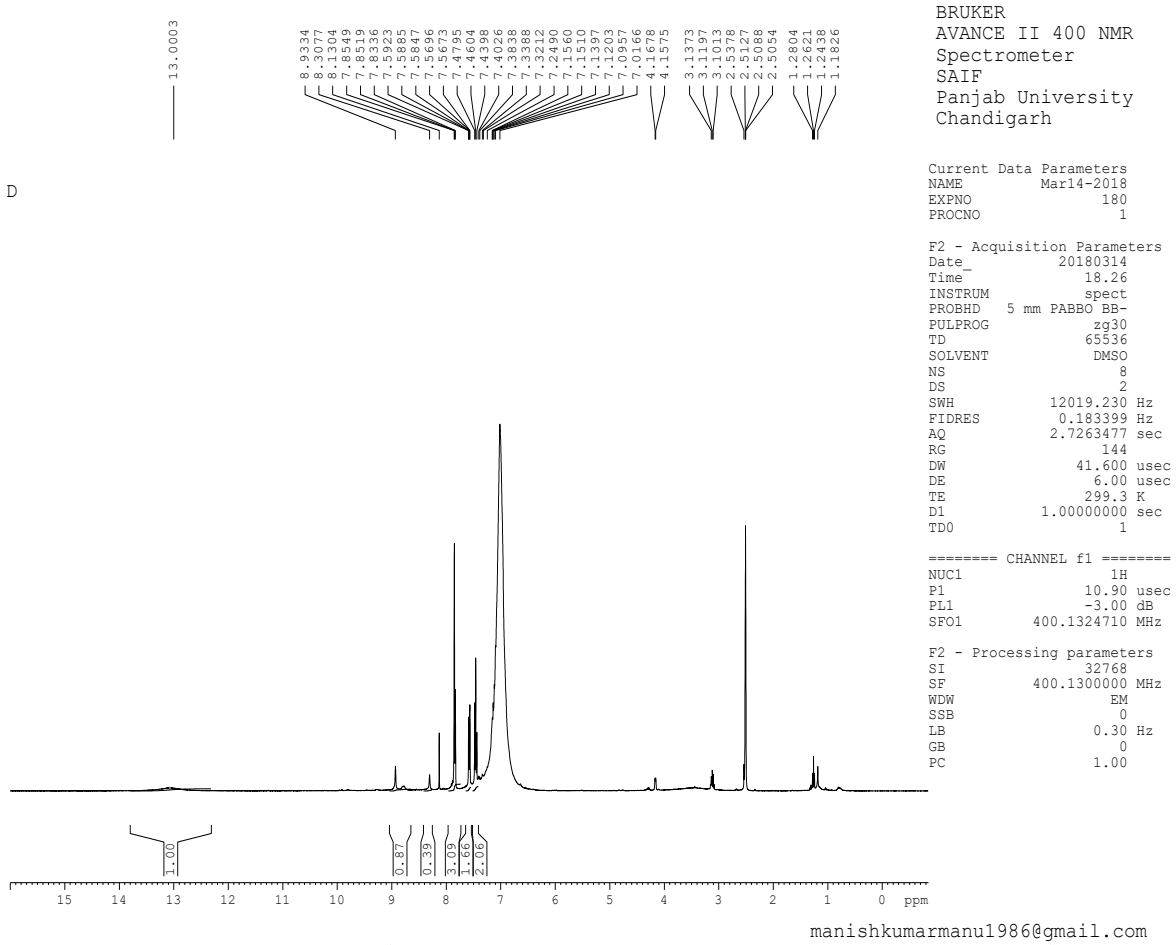


(3-Chloro-benzylidene)-(4-phenyl-thiazol-2-yl)-amine

Experimental Section

General Conditions: Melting points were discovered using open capillary tubes and are uncorrected. Iodine spotting and TLC were applied to the silica gel-G surface. Nicolet 5ZDXFT-IR spectrometers in the KBr phase and Brucker WP 200 and 500 SY spectrometers in the 1H NMR phase were used to record the IR spectra. Preparation of [(3-chloro-benzylidiene)-4-phenyl-thiazole-2-yl)-amine: general technique (3a) In the presence of HCl, (0.001mole) 2- amino 4- phenyl thiazole and 0.70gm of 3- chlorobenzaldehyde were refluxed for three to four hours. The product, M.P.-150-154^{0}C, was obtained from the resultant solid after it had been filtered, cleaned, and recrystallized from ethanol. 3a: 1HNMR: 2.6 (s,1H, CH3), 7.2-8.7 (m, 10H, Ar-H), IR (KBr): 1575 cm-1 (C=N)

IR Data



Sr. No.	Frequency in cm^{-1}	Assignment	Literature value cm^{-1}
1	3194.26	Ar -H	3300-2900
2	1608.70	C=N stretching	1640-1690
3	1473.68	C=C stretching	1400-1500

Antioxidant
Ferric reducing antioxidant power assay
Reducing power assay method for determination of antioxidant activity/ potential of samples
Procedure:-

Different concentration of the drug (10-50ug/ml) was added to 2.5 ml of 0.2M sodium phosphate buffer (pH 6.6) & @.5ml of 1% potassium ferricynide [K3Fe(CN)6] solution. The reaction mixture was vortexed well & then incubated at 50^0 C for 20 min using vortex shaker. At the end of the incubation , 2.5 ml of 10% trichloacetic acid was added to the mixture and centrifuged at 3,000 rpm for 10min. The supermantant (2.5ml) was mixed with 2.5 ml of deionized water & 0.5ml of 0.1% ferric chloride. The coloured solution was red at 700nm against the blank with reference to standard using UV Spectrophotometer. Here, ascorbic acid was used as a reference standard.

The percentage of radical scavenging (%) was calculated by the following formula:

$$\textbf{\% Free radical scavenging activity} = A_c - A_s / A_c \times 100$$

Where , A_c = Absorbance of control at 720 nm

A_s = Absorbance of sample

The concentration of sample required to scavenge 50% of the DPPH free radical (IC_{50}) was determined from the curve of percent inhibitions plotted against the respective concentration.

Experimental

Absorbance should increses with increses in concentration. Results confirm the reducing power Of samples which increased with increasing concentration. Higher value absorbance of the reaction mixture indicated greater reduing power. The redusing power was found to be on oreder Br>NO2.

Table 1 Ferric Reducing Antioxidant Power Assay

Standard Observation - (Ascorbic acid) (720nm)

Concentration(ug/ml)	**Absorbance 1**	**Absorbance 2**	**Absorbance 3**
10ug/ml	0.002	0.006	0.061
20ug/ml	0.395	0.251	0.029
30ug/ml	0.941	0.775	0.499
40ug/ml	1.451	1.350	1.036
50ug/ml	2.000	2.000	2.000

Control Absorbance - 0.812 (720nm)

Sample Observation- (720nm)

Formula –

$$\textbf{Scavenged(\%)} = (A_{cont}) - (A_{test}) / (A_{cont}) \times 100$$

Table2 (% Scavenged of DPPH free radical)

Sample name	**Concentration**	**Absorbance**	**%Scavenged**
4a (H)	a) 30ug/ml b) 50ug/ml	0.121 0.305	72.1 %
4b (OCH_3)	c) 30ug/ml d) 50ug/ml	0.213 0.504	68.2 %
4c (NO_2)	a) 30ug/ml 50ug/ml	0.068 0.463	62.9%

4d (Br)	e) 30ug/ml f) 50ug/ml	0.171 0.629	17.1%
4e (Cl)	a) 30ug/ml b) 50ug/ml	0.058 0.102	21.2%

Results and Discussion

Several five member aromatic systems having three hetero atoms at symmetrical position 1,3,4-thiadiazole had been studied because of their interesting physiological properties. Specifically substituted benzaldehyde or naphthaldehyde were combined with 2-amino-5-diethylamino-pentane in an equal amount of methanol to produce the desired Schiff-base phenols or Schiff base naphthalene ligands for evaluation [19]. Furthermore, by reducing their corresponding Schiff-base counterparts with KBH4 at 80°C for 3 hours, substituted amine phenol or amine naphthalene ligands were also produced [20].

All compounds underwent standard analytical procedure purification and characterization. The spectral and analytical data for digits 1 through 7 agreed with the suggested formulation. By measuring the incorporation of 3 H hypoxanthine, we assessed 1-7's capacity to prevent the formation of trophozoites in intraerythrocytic culture [21]. A more accurate way to quantify parasite development is through the inhibition of hypoxanthine incorporation, which correlates well with direct blood smear counts. Unfortunately, neither the CQ-sensitive (HB3) nor the CQ-resistant (Dd2) strains were significantly affected by compounds 1, 2, 3, 4, and 6. The moderate half-maximal inhibitory concentration (IC50) values for the active compounds 5 and 7 against CQ-sensitive lines, respectively, were 5.53 and 6.38 M. However, compound 7 was found to be twice as effective as compound 5 against CQ-resistant Dd2 lines (IC50, 3.5 M for compound 5; 1.7 M for compound 7).

The structural differences of compounds 5 and 7 may be responsible for their varied biological actions. The quinoline ring of the CQ, which lacks chlorine at position 7 and the quinonyl basic nitrogen, has a simple substituted aromatic ring in position 5, but the quinoline ring of the 7 contains a naphthalene ring. Furthermore, it has been demonstrated previously that nitrogen atoms of side chain in chloroquine and aromatic ring assist in accumulation of the drug within the digestive vacuole of the parasite (Vydac) employing an eluent mixture of methanol and water (100% water for first 5 minutes, followed by a change to 50 : 50 (Water : MeOH) for the next 5-20 minutes, and finally 100% MeOH for the next 20-25 minutes). The retention times (Rt) are given for selected compounds.

Absorbance should increses with increses in concentration. Results confirm the reducing power Of samples which increased with increasing concentration. Higher value absorbance of the reaction mixture indicated greater reduing power. The redusing power was found to be on oreder Br>NO2.

Acknowledgment:

The Authors are very thankful to the Department of Chemistry S. P. M. Science and Gilani Arts, Commerce College Ghatanji and Shri Shivaji Science College Amravati for provide the necessary facilities in the laboratory. Words of gratitude are also expressed for SAIF/RSIC Chandigarh for IR and NMR spectral data.

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35

Synthesis and Characterization of Schiff Bases Using Different Amines and their Biological Activities

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Nowadays, the research field dealing with Schiff base chemistry has expanded enormously. The importance of Schiff base for bioinorganic chemistry, biomedical applications, supramolecular chemistry, catalysis and material science, separation and encapsulation processes, and formation of compounds with unusual properties and structures has been well recognized and reviewed. They also serve as a back bone for the synthesis of various heterocyclic compounds. Schiff bases have been utilized as synthons in the preparation of a number of industrial and biologically active compounds like formazans, 4-thiazolidinines, benzoxazines, and so forth, via ring closure, cycloaddition, and replacement reactions. Schiff base are organic compounds possessing azomethine group which resulted from condensation of amine with aldehyde or ketone. Schiff base derived from aromatic amine and aromatic aldehydes have a wide variety of application such as biological activity, catalytic activity and also used as ligands to obtain metal complexes because of their excellent abilities of this type of Schiff base are widely used as anticorrosion for different metals in different media. The synthesis and characterization of transition metal complexes of schiff bases containing nitrogen and oxygen donors atoms has increased manifold in the recent past .The Schiff base ligands are considered to be good chelating agents [3], Schiff bases are a special class of ligands with a variety of donor atoms exhibiting interesting coordination modes towards transition metals, and azomethine linkage is responsible for the biological activities. The Schiff bases derived from various amines have been widely investigated and find applications in biomimetic catalytic reactions, materials chemistry and industry. Schiff base complexes have also gained attention as stereo chemical models in transition metal coordination chemistry due to their structural variety.

Key Word:- Synthesis, Schiff Bases, Biological Activity.

MATERIALS AND METHOD

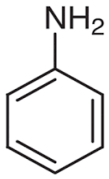
Preparation of Schiff Base by using different substituted aromatic amines with substituted aromatic benzaldehyde. Following materials and method is included.

MATERIALS

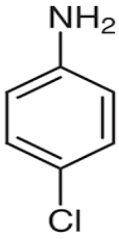
Materials Required are -

Substituted Aromatic Amines such as Aniline, p-chloro Aniline,

ANILINE-Aniline appears as a yellowish to brownish oily liquid with a musty fishy odor.melting point -6°C; boiling point 184°C;flash point 158°F. Denser than water(8.5lb\gal)and slightly soluble in water. Vapours heavier than air. Toxic by skin absorption and inhalation.Produces toxic oxides of nitrogen during combustion. Used tomanufacture other chemicals, especially dyes, photographic chemicals ,agricultural chemicals and others.

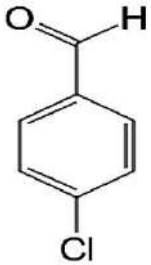


P-CHLORO ANILINE-4-Chloro aniline is a chloroaniline in which the chloro atom is para tothe aniline amine group.It is member of monochlorobenzenes. P-chloroaniline appears as a white or pale yellow solid.Melting Point is 69.5℃.



Substituted Aromatic Benzaldehydesuch as 4-chloro Benzaldehyde

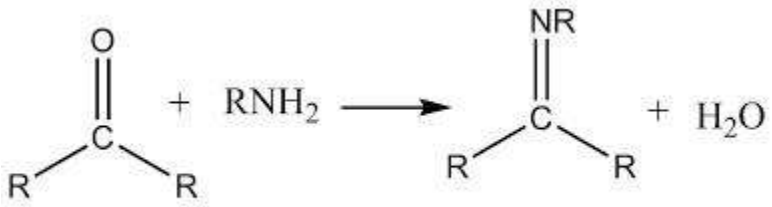
4-CHLOROBENZALDEHYD



-4-Chloro Benzaldehyde appears as colourless to yellow powder or white crystalline solid.It has pungent odour.

GENERAL METHOD FOR PREPARATION OF SCHIFF BASE-

The mixture of different substituted aromatic amines and substituted aromatic benzaldehyde was dissolved in methanol . These solution was acidified and reflux for about 5-6 hrs. The excess of solvent was removed under pressure. The resulting compound was washed, dried and crystallized.



(Schiff base)

ANTIMICROBIAL ACTIVITY OF SCHIFF BASE

The synthesized schiff bases were screened in vitro for their antibacterial activities against Escherichia coli (E.coli) and Bacillus subtilis (B. subtilis) bacterial strains using well diffusion method. The bacterial cultures were incubated at 30± 0.1℃ for 24 hours by inoculation into nutrient agar.Schiff bases were stored dry at room temperature and 3ml ethanol. Antibacterial activities of each compound were evaluated by the agar disc diffusion method. Muller hinton agar media (15 cm^3) kept at 45℃ was poured in the petri dishes and allowed to solidify poured petri plates were streaked with culture media wells formed prepared schiff bases (100µl) were applied on the solid ager media by pressing tightly. The petri plates were placed at 37℃ for 24 hours.At the end of period the inhibition zones formed on media were measured with zone reader millimeters.

SAMPLE	Conc. (µg/ml)	GRAM POSITIVE E. coli	GRAM NEGATIVE B. subtilis
N-(4-CHLOROBENZYLIDENE ANILINE) (1C)	100µL	10mm	12mm
	100 µl	-	13mm
N-(4-CHLORO BENZYLIDENE)-4-CHLORO ANILINE (2C)	100µl	10mm	16mm
	100 µl	-	14mm

Antibacterial activities against Schiff compound at concentration 100µl/ml.

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36
Physico-Chemical Assessment of Soil Sample in Jarud Region in Amravati District of Maharashtra (India)

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ABSTRACT

Soil is a natural body of mineral and organic material differentiated into horizons, which differ among themselves as well as from underlying materials in their morphology, physical make-up, chemical composition and biological characteristics. In the present research work, studies on soils with physical properties, chemical properties and micronutrients of soils have been done. Soil samples were collected from two different locations covering Jarud, in Warud Tahsil in Amravati District (Maharashtra) India. The soil parameters like soil colour, moisture, pH, Carbon, Nitrogen, Copper, Potassium, Phosphorous, Zinc, Boron, Copper and Sulphur content, were analyzed in the month of March 2022. The values of pH indicated that all samples of the soils are alkaline, all samples were containing moderate amount of available micronutrients**.**

Keywords: Physico-Chemical analysis, Parameters, Jarud Village, Plants Nutrients.

INTRODUCTION

To improve soil, plant health and soil balance to optimize production, it's important to identify the soil's biological, mineral, chemical and physical requirements. When evaluating the soil analysis, we look for synergies and approach mineral and microbe plant and pest management holistically to provide the formula for nutrient, trace elements and biological inputs to achieve true soil balance. The soil analysis report provides the information necessary to set nutrient application targets, which are used to calculate manure and fertilizer application rates. Test results from regular field sampling (particularly from benchmark sites) allow monitoring and detection of changes in soil parameters (e.g., nutrients, pH, and salinity) with time.

Soil analysis provides us the background knowledge on soil available nutrient status along with some physico-chemical and biological properties; that we need in order to take specific decisions on balanced and integrated nutrient management for healthy soils and crops. The quality and health of soil determine agricultural sustainability and environmental quality which jointly determines plant, animal and human health. The status of available micronutrients in soils and their relationship with various physico-chemical properties have been attempted by several investigators (1-2). Considerable research work has been done regarding the study of Nutrients and Physico-Chemical assessment of various types of soil in Maharashtra as well as in India (3-4) but the investigation of nutrients and parameters of soil of Jarud village in Amravati district in Maharashtra.

Physico-chemical characteristics of some samples of soil from some farms of nearby villages of Kannad taluka, Dist. Aurangabad (5). Abhishek Jangir et. al. (6) evaluates the major and micronutrient status of Kelapur block, Yavatmal district, Maharashtra. Wodaje Addis et. al. (7) carried out assessment of some selected physicochemical parameters in soil samples collected from four agricultural areas of East Gojjam Zone (Debrem Markos, Dejen, Bichena

and Debre (Werk), Ethiopia. Perveen et. al. (8) has studied micronutrient status of soils and their relationship with various physico-chemical properties. Khadke et. al. (9) reported soil analysis and its environmental impact on Nanded city of Maharashtra State. The impacts of industrial pollution on the ground water soil and plant have also been reported in our country and abroad (10). Investigation of some parameter and Nutrients from Soil samples of Rice field by Jadhav et.al. (11). Geeta Tewari et. al. (12) carried out the physico-chemical properties of soils from different land use systems viz. agriculture, olericulture and two dominant forest types.

R. Zornoza et al (13) studied the Soil quality (SQ) assessment has long been a challenging issue, since soils present high variability in properties and functions. K. Senthilarasan et. al. (14) worked on soil analysis to study physical properties and micronutrients of soils. Soil samples were collected from five different locations covering Nagapattinam district (south) in tamilnadu. Joshi et al. concluded that India Soil salinity greatly affects growth and development of vegetation (15), but the investigation of nutrients and parameters of Soil of Jarud village in Warud Tahsil of Amravati district in Maharashtra, India was still lacking.

EXPERIMENTAL

Study Area

Mauja Jarud (part2) is a small village in Warud Tahsil of Amravati District (Maharashtra State). This area is well known for orange, cotton and Toor. The sources of water for this area are of well. Relative to its geographical location, the study area enjoys a tropical type of climate.

Collection of Samples

Soil samples were collected randomly at 0 to 15 cm and 15 to 30 cm depths with five plots (field), five samples from each plot (field) respectively, in well sterilized polythene pouches. Soil sample were collected from following Farmers fields.

1) Sample 1 (TMG-1) was collected from Mr. Manikrao Sitaramji Ghotkar field.

2) Sample 2 (TMG-2) was collected from Mr. Raju Devrao dathe field.

Table-1: Nutrients and Physico-Chemical assessment of Soil Samples.

Analysis of Parameters			
Sr.No.	**Parameters**	**TMG-1**	**TMG-2**
1	Colour	Black	Whitish Black
2	pH	7.41	7.42
3	Organic Carbon (%)	0.46	0.45
4	Nitrogen	210	200
5	Phosphorous (kg/hect.)	28	31
6	Potassium (kg/hect.)	340	350
7	Mn (ml/gm/kg)	8	7
8	Fe (ml/gm/kg)	39	39
9	Zinc (ml/gm/kg)	3.1	3.1
10	Boron	1.5	1.5
11	Copper	8	9
12	Sulphur	59	59
13	Salinity	0.2	0.2

Determination of Physical Parameters

Reagents uses for this research work were AR grade and chemicals other than reagent are LR grade manufactured by S.D. fine, LOBA and Merck. The soil samples were dried for about 24 hr. and grinded more finely. In this work about thirteen physico-chemical parameters and nutrients of two soil samples were determined and results were also recorded. During collection, temperature of the sample was recorded.

Following methods were used for estimation of various parameters are:

i. Determination of Moisture: by Weighting Method.
ii. Determination of pH: by Digital pH Meter
iii. Determination of Organic Carbon: by Titration Method
iv. Determination of Copper (Cu): by Atomic Adsorption Spectroscopy.
v. Determination of Nitrogen (N): by Titration Method
vi. Determination of Phosphorous (P): by Titration Method
vii. Determination of Potassium (K): by Flame Photometry
viii. Determination of Color of Soil: by Viewing soil

RESULTS AND DISCUSSION

Colour

The soil sample TMG-1 was black in colour and sample TMG-2 was whitish black in colour.

Moisture

Moisture content value ranges from 1% - 4%. It is clear from the result that Soil sample TMG-1and TMG-2 has 2.5 and 3.7% moisture respectively.

pH

pH was medium quantity in the ranges 7.41 to 7.42. To dig drains, to make out flows, sowing green crops, cow manure to burry plant wastes, to supply necessary amount of water, use of gypsum is need.

Organic carbon

Organic carbon contents were recorded in the range 0.46-0.45 %. The soil sample TMG-1 and TMG-2 has medium organic carbon.

Nitrogen

Available Nitrogen quantity ranged from 200– 210 Kg/hect. The soil sample TMG-1 and TMG-2 has less Nitrogen content.

Phosphorous

Available Phosphorous was medium quantity ranged from 28-31kg/hect. The soil sample TMG-1 have less Phosphorous as compared to TMG-2.

Potassium

Available Potassium quantity ranged from 340-350 kg/hect. The soil sample observed value for potassium was medium.

Zinc

The Zinc was less in quantity in both TMG-1 and TMG-2 i.e 3.1 ml/kg.

Copper

Copper content is soil sample ranges from 8-9. It has been seen that in soil sample TMG-1 and TMG-2 has approximate quantity of copper.

Boron

It has been seen that in soil sample TMG-1 and TMG-2 has 1.5 ml/gm/kg of Boron. Both the soil sample contains approximate Boron quantity.

Sulphur

It has been seen that in soil sample TMG-1 and TMG-2 has 59 ml/gm/kg of Sulphur. Both the soil sample contains approximate Sulphur quantity.

CONCLUSION

In the soil sampleTMG-1and TMG-2, the pH becomes middle alkali and to increases the pH of this soil suggested the use of compost manure. Then recommendation of to dig drains, to make out flows, sowing green crops, cow manure to bury plant wastes, to supply necessary amount of water, use of gypsum. In the soil sampleTMG-1 and TMG-2, Zinc becomes less, then recommendation zinc sulphate10 kg / hectare. In the soil sample TMG-1 and TMG-2 the potassium become medioum, then recommendation Potash 400gm / hectare. In the soil sample TMG-1 and TMG-2 the phosphorous is middle. To increase the crop quality phosphorous will be given through fertilizer 2000 gm /hectare. In the soil sampleTMG-1 and TMG-2, Boron becomes approximate. Organic fertilizer from goat manure resulted in the highest yield per hectar in groundnut and total biomass in palm oil plant. In the soil sampleTMG-1 and TMG-2 sulphur become approximate. In the soil sample TMG-1 and TMG-2 medium organic carbon and nitrogen. So, to increase more yield of crop by using carbon and nitrogen to soil in the form of compost manure.

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37

Synthesis ,Characterization And Antimicrobial Study Of Co(II),Cu(II) and Fe(III) Complexes Of Substituted 4,4'- Dimethoxybenzoinhydrazones

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Abstract: Metal benzoinhydrazone complexes have been synthesized from substituted benzoinhydrazone were carried out by the known literature method.The structure of all the synthesized compounds were justified on the basis of chemical characterized by elemental and spetral analysis. The Physico-Chemical data suggest octahedral geometry for Co(II) & Cu(II) complexes. The synthesized complexes were screened for antimicrobial activity at a concentration of 1000µgm/ml.Which was serially diluted to determine their MIC values.

Keywords:- Metal complexe, 4,4'-Dimethoxybenzoinhydrazones, sodiumhydroxide DMF-Water(80%) medium, Antimicrobial Activity , spectral analysis.

Introduction:-

The complex formation of benzoinhydrazone with copper(II) and nickel(II) , were synthesized by scherbakov[1] .Prasad[2] , studied by the synthesis of Novel(II) complexes with now ligand derived from hydrazone of isoniazid and their magnetic-spectral, electrochemical, thermal and antimicrobial investigation. Benzoinhydrazone are well known for their biological activity coordination compounds containing ONS as donor atoms are reported to antimicrobial activity[3]. Synthesis, spectral and biological studies of Co(II), Ni(II), Zn(II), Cu(II) and Cd(II) complex with benzyl salicyladehyde acyldihydrazone were carried out by singh[4]. The simultaneous spectroscopic determination of palladium and osmium with salicyladehyde hydrazone was carried out by Ray[5]. The synthesis and structural characterization of three new co-ordination complexes of Co(II), Mn(II) and Cu(II) with N,N,O- donor hydrazine ligands were carried out by shit[6] .The coordination chemistry of hydrazones is an intensive area of study and numerous transition metal complexes of these ligands have been investigated[7]. Synthesis and characterization of some copper(II) complexes with N,S,O-donor thiohydrazones were carried out by Dey[8]. The important reactions of carbonyl with hydroxylamine, semicarbazide and various hydrazines were briefly studied in presence of strong base in ethanol medium.[9-14].While furoinbenzoinoximes, furoinbenzoin hydrazone, furoinphenyl hydrazone and furoinbenzoin semicarbazone were synthesized by the interaction of furoinbenzoin with hydroxylamine hydrochloride, hydrazine hydrate, phenyl hydrazine and semicarbazide hydrochloride in presence of aqueous sodium hydroxide in DMF-Dioxane-water (80%) medium respectively.

Experimental:-

The 4,4'-Dimethoxybenzoinhydrazones was prepared by refluxing substituted benzoine with hydrazine hydrate in presence of alkaline medium for 3-4 hours this reaction mixture was kept overnight. This solid products formed were isolated and washed several times with water alcohol mixture the purity was checked by TLC paper. Their structural details were confirmed on the basis of elemental and spectral analysis.In order to Synthesize the complexes the equimolar mixture of each of the ligand(0.01M) and metal salts(0.01M) were refluxed on a water bath for 6,8 hours in presence of sodium acetate in ethanol . The reaction mixtures was kept overnight. The product formed were isolated washed several times with cold water ethanol

mixture. The characterization of synthesized complexes was made with elemental analysis, IR and UV-VIS spectra.

Result and Discussion

TABLE-1

THE METAL COMPLEXES COMPOUND,MOLECULAR WEIGHT, COLOUR AND ELEMENTAL ANALYSIS OF VARIOUS METAL IONS

Complexes	Colour	Molecular wt	Elemental analysis Found/(calculated)%			
			C	H	N	M
4,4'-DMBH-Co(II)	Pale	682.93	55.30 (56.22)	4.93 (5.85)	8.19 (8.19)	7.71 (8.62)
4,4'-DMBH-Cu(III)	Brown	687.54	54.90 (55.84)	4.87 (5.81)	8.14 (8.14)	8.30 (9.24)
4,4'-DMBH-Fe(III)	Brown	627.84	60.24 (61.16)	4.86 (5.73)	8.91 (8.91)	7.96 (8.89)

TABLE-2

IR SPECTRAL DATA OF LIGANDS AND ITS METAL COMPLEXES

Ligands and its Complexes	υ(O-H)	υ(C=N)	υ(C-O)	υ(M-O)	υ(M-N)
4,4'-DMBH	3388	1634	1362	-	-
4,4'-DMBH-Co(II)	3351	1614	1308	466	578
4,4'-DMBH-Cu(II)	3327	1618	1317	520	585
4,4'-DMBH-Fe(III)	3378	1610	1249	471	565

The IR spectra of lignad shows a strong band at 1634 cm^{-1} due to (C=N) group broad band around 3388 cm^{-1} in the spectra of complexes is assignable of water.4,4'-DMBH-Co(II) shows band at 3388 (O-H).Which decreases 3351cm^{-1} inducting that attached to oxygen .However 1634 (C=N) significantly decrease to 1614 cm-1 showing linkage through azido nitrogen.The υ(M-O)& υ(M-N) vibration are verified to existing by the appearance of new weak bands in the spectra of complexes at 578 & 565 respectively.

TABLE-3
ELECTRONIC SPECTRAL DATA,MAGNETIC MOMENT AND LIGAND FIELD PARAMETER OF THE METAL COMPLEXES

Complexes	μeff (B.M.)	λmax (cm-1)	Dq	B	CFSE	% Cova	$(\Lambda_M)\Omega^{-1}$ Cm^2 Mol^{-1}
4,4'-DMBH-Co(II)	4.72	13604,19018, 23023	1492	0.737	205	26.03	9.5
4,4'-DMBH-Cu(II)	1.79	13698,18587, 22984	1492	0.737	205	26.29	10.8
4,4'-DMBH-Fe(III)	5.67	13888,17979, 22471	1514	0.646	346	35.04	11.4

The electronic spectrum of Co(II) complexes exhibits three bands at 13604,19018 and 23023 cm^{-1} which may be assigned to $^4A_{2g} \dashrightarrow {}^4T_{2g}(F)$,$^4A_{2g} \dashrightarrow {}^4T_1g$ (F) and $^4A_{2g} \dashrightarrow {}^4T_1g(P)$,transition, respectively for an octahedral stereochemistry[11] .The magnetic moment value of 4.72 B.M for Co(II) complex is consistent with octahedral geometry around metal centre. Fe(III) Complexes three bands are observed in case of Fe(III) complexes at 13888,17979,22471 cm^{-1} which may be assigned to $^6A_{1g} \dashrightarrow {}^4T_{1g}(F)$,$^6A_{1g} \dashrightarrow {}^4T_2g(F)$ and $^6A_{1g} \dashrightarrow {}^4Eg$, belongs to transition respectively, indicating octahedral geometry of Fe(III)complexes [12-13]. The value of 5.67 B.M. would suggest high spin six coordination for Fe(III) complexes. The values of various ligand field parameters 10Dq ,B ,λmax, CFSE and conductance respectively favoring in octahedral geometry for this complex.

ANTIMICROBIAL ACTIVITY OF COMPLEXES

The compounds were assayed for their antimicrobial activities[14] against four test organisms E.coli, S. aureus, Ps.aeruginosa, B. subtilis at a concentration of 1000 μgm/ml by agar well technique[15]. Further their MIC value against these organisms were determined by serial dilution method using DMF as a solvent. The results obtained are given in table-5

TABLE-5

MIC VALUES IN μgm/ml OF COMPOUNDS

Complexes	E.coli	S.aureus	P. aeruginosa	B.Subtilis
4,4'-DMBH-Co(II)	125	250	125	125
4,4'-DMBH-Cu(III)	125	63	63	63
4,4'-DMBH-Fe(III)	125	250	125	125

On the basis of MIC values, 4,4'-DMBH-Cu(II) is found to be most effective antimicrobial agent followed by 4,4'-DMBH-Co(II) and 4,4'-DMBH-Fe(III).The enhance antimicrobial activity in case of the compounds. 44'DMBH-Cu(II) showed the lowest MIC values(i.e 63µgm/ml) against maximum number of microorganisms.

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38

Study of Extraction and Chemical Screening of *T. cordifolia* (Guduchi) Stem & Leaves

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Abstract:

The water & ether extracts of T.codifolia Stem & leaves were prepared- the total ash found to be 6.861. The leaves show dark yellow fluorescent colour with picric acid the extracts were tested for some phytochemicals. T.cordifolia commonly named as "Guduchi" is known for its immense application in the treatment of various diseases in the traditional ayurvedic literature. Recently the discovery of active components from the plant and their biological function in disease control has led to active interest in the plant across the globe. Encompasses (i) the genetic diversity of the plant and (ii) active components isolated from the plant and their biological role in disease targeting. The future scope of the review remains in exploiting the biochemical and signaling pathways affected by the compounds isolated from *Tinospora* so as to enable new and effective formulation in disease eradication.

Keyword: T.Cordifolia, Flourescent Test, Ether Extraction, Water Extraction, Antimicrobial activity.

INTRODUCTION:

The possibility of outbreak of severs acute respiratory syndrome (SARS) and Bird Flu Virus continuing spread of HIV/AIDS and emergence of resistant pathogenic strains against current medication compel investigators to look for new protective measure against these threats. Immune activation is an effective as well as protective approach against emerging infection disease [(1)]. T.ordifolia commonly known as guduchi, heart-leaved moonseed and giloya is a herbaceous vine of the family Menispermaceae, is a glabrous climbing succulent shrub. It is native to India, easily in the tropical region. It is widely used in Ayurvedic medicine in India as well as tonicuitalizer and as a remedy for diabetes mellitus and metabolic disorders, [(2)] the fundamental role of innate immunity in host defense is becoming clearer as analysis of human genome continues to identify new genes serving innate immune function. Innate immune activations immune response antigen- specific T & B lympocytes [(3, 4)] Cytokines play crucial roles in requlating various aspect of immune response. Among cytokines interleakin IL-12 plays a central role in co-ordinating innate and cell mediated adaptive immunity ,[(5)] Immune stimulation can provide both prophylalactic as well as postexposure protection [(6)]. Dementia is a syndrome of failling memory and other intellectual functions with little or no disturbance in consciousness. Degeneration of the cerbral neurons is one of the commonest and vital causes for dementia with increasing age, there by leading to deterioration in quality of life in elderly. Hence a greater research is required in early diagnosis of the condition and development of newer effective drugs to prevent or halt the progression of the disease. This is possible by basic understanding of learning and memory process [(7)]. Medicines derived from plants have played a pivotal role in health care of ancient and modern cultures. Ayurveda, the Indian system of medicine mainly uses plant based drugs or formulations to treat various ailments including cancer. Recent surveys suggest that one in three Americans uses dietary supplements daily and the rate of usage is much higher in cancer patients, which may be up to 50% of patients treated

in cancer centers [8]. Many synthetic or natural agents have been investigated in the recent past for their efficacy to protect against radiation damage.1 Among the natural radioprotective agents compounds, cystine, cysteamine, 5-hydroxytryptophan, 5-hydrox- ytryptamine, glutathione, and vitamins like A, C, and E2 have been extensively studied. Important synthetic molecules include amino-ethyl-isothiouronium bromide hydrobromide (AET), WR-272 1. However, the inherent toxicity of these agents at the radioprotective concentration warranted further search of a safer and effective radioprotector. To reduce toxicily, a strategy of combining radioprotective molecules working through different modes of action has also been attempted.Three in fact, no radioprotective agent now available, either singularly or in combination, meets all the requisites of an ideal radioprotector. Four recently several isolated plant products and crude extracts that may have a natural combination of several bio-active molecules capable of giving radioprotection through different mechanisms, have been investigated [9].

EXPERIMENTAL: - Fresh healthy leaves and stem of T.cordifolia were collected .They were washed thoroughly with distilled water and dried in shade for seven day followed by grinding to make powder of the same size and stored in air tight bottles.

Total Ash: About 10 g of powdered leaves & stem was accurately weighed and taken in a silica crucible, which was previously ignited and weighed. The powder was spread as a fine, even layer on the bottom of the crucible. The crucible was incinerated gradually by increasing temperature to make it dull red hot until free from carbon. The crucible was cooled and weighed. The procedure was repeated to get constant weight.

Acid Insoluble Ash: The ash obtained as described above was boiled With 25 ml of 2N HCI for five minutes. The insoluble ash was collected on an ash less filter paper m and washed with hot water. The insoluble ash was transferred into a silica crucible, ignited and weighed. The procedure was repeated to get a constant weight

Water Soluble Ash: The ash obtained as described in e determination of total ash was boiled for 5 minutes with 25 ml of water. The insoluble matter was collected on ash less filter paper and washed with hot water. The insoluble ash was transferred into silica crucible, ignited for 15 minutes, and weighed. The procedure was repeated to get a constant weight. The weight of insoluble matter was subtracted from the weight of the total ash. The difference of weight was considered as water-soluble ash the result of total ash, acid insoluble ash, water soluble ash and other physical Para meters of T.cordifolia leaves are summarized in Percentage of ash and Chemical Screening.

Antimicrobial Activity: Antimicrobial activity of T.cordifolia plant was determined against bacterial strain, salmonella typnis Escherichia Coil, Staphy Lococcus acereus Bacillus subtilis by well diffusion assay on agarr plate.The bacterial culiure were grown on nutrient broth for 24 hrs. The activity grown cullirs were spread on nutrient agar plates by spread plate method well were prepared by brose sample was poured in the well. Streptomycin antibiotic is used as standard 100 mg 1 ml concentration.

WATER EXTRACTION: 10 gm of sample (Tinospora plant) was taken in round bottom flask. 35ml of distilled water was added. Water condenser was arranged. Refluxed for 3 hrs after complete heating the water extract was cooled. Solution was filtrated throught whatman paper No. 42 Residue was dried and weight was took and water soluble compound was calculated.

ETHER EXTRACTION: 10 gm of leaves & stem sample was taken Tinospora plant (10 gm each) was extracted using Round bottom flask, soxhlet apparatus was arranged. The extracts

were too dried to yield crude residue. The extracts were auto-calved and stored at 5^0c until further use. Ether soluble compound was calculated.

RESULT & DISCUSSION : In study of three crude extracts of leaves and stem of T.Condifolia have been investigatged, aqueous either and water extraction were tested for their total Fluonaid contents microbial activity performed by using assay of reducing powder of Tinospora plant.

Percentage of ash

Sr. No.	Sample (ash)	Percentage
1.	Total Ash	5.78%
2.	Water Soluble	28.03%
3.	Acid Insoluble	59.00%

Chemical Screening

Sr. No.	Chemical Screening	Water Extraction	Ether Extraction
1.	Tannins	+ve	-ve
2.	Saponins	-ve	+ve
3.	Phenols	+ve	+ve
4.	Flavonoids	-ve	-ve
5.	Alkaloids	-ve	+ve

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39

In-silico QSAR-based virtual screening recognition of novel anaphylactic lymphoma kinase inhibitor

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Abstract: The goal of this work is to find a new treatment option that blocks ALK tyrosine kinase. We used drug repositioning and a QSAR-based virtual screening method together in this work to find a new lead drug candidate that might be able to stop ALK tyrosine kinase receptors. Molecular docking, MD modelling, and MMGBSA studies were used to look into how the new FDA-approved drugs interact with each other. To make sure the results we got online were correct, we used the A549 lung cancer cell line to do an in vitro MTT test. The usual method suggested by the OECD is used in this study. It includes QSARINS GA-MLR models, QSAR-based virtual screening of about 1652 FDA chemicals, MD simulation, and MMGBSA analysis using Desmond software. The MTT test confirmed what was found in the computer model. The QSAR model that was made meets a number of validation standards, such as R^2 = 0.79, Q^2_{LOO} = 0.78, Q^2_{LMO} = 0.78, R^2_{ex} = 0.77, and CCC_{ex} = 0.87. Using QSAR-based virtual screening, we also found 12 FDA drugs that were hits in the computer. Some of these substances could be used as ALK-TK inhibitors in clinical settings because their docking values ranged from -7.10 to -10.57 kcal/mol. The A549 cancer cell line was used in the MTT test to support the results that were found in a computer programme. The QSAR-based virtual screening indicated that the new molecule ZINC000150338819 would have a $_pIC_{50}$ of 9.18 M. This drug has both wild-type and mutant ALK-TK. The molecule got a docking score of -10.57 kcal/mol and an RMSD of 1.54Å as well. The ZINC000150338819-ALK TK complex is stable, and it includes both wild-type and mutant ALK TK. This was proven by MD modelling and MMGBSA tests that lasted 200 ns. To confirm the results from the computer simulation, the MTT test shows that Ledipasvir had more inhibition than ceritinib. It is suggested in this study that the chemical ZINC000150338819 could be used as an ALK TK inhibitor in the drug development field.

Keywords: OECD; GA-MLR; MD simulation; MMGBSA; X-Ray.

1 Introduction

In 1991, researchers discovered a membrane-bound tyrosine kinase receptor called anaplastic lymphoma kinase (ALK). Abnormal forms of ALK, such as fusion proteins, point mutations that activate ALK, and gene amplification, are found in cancer. Abnormal ALK expression is linked to the development of many types of cancer [1]. The human ALK gene is located in the chromosomal region 2p23.2p23.1. This 26-exon gene encodes the ALK protein, which is 1620 amino acids long. The full-length ALK protein has a transmembrane region, a ligand-binding region, and an intracellular tyrosine kinase region consisting of 561 amino acids[2,3]. The 3-tyrosine motif (Tyr1278, Tyr1282, and Tyr1283), where autophosphorylation for kinase activity occurs, is also found in other members of the same family of kinases (**See fig.1**).

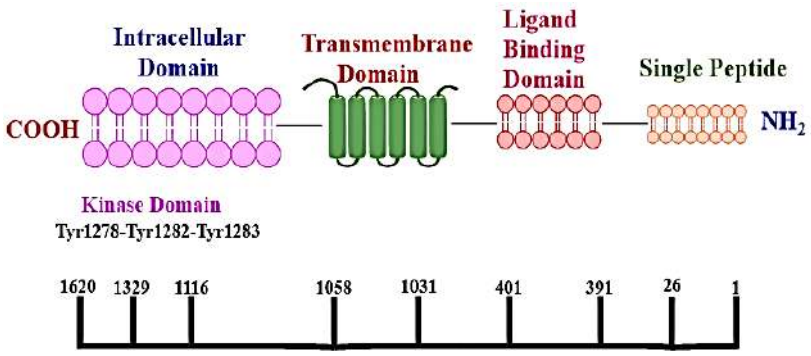


Figure 1 Structure of ALK, showing a polypeptide of 1620 amino acids. The full-length form of ALK resembles other receptor tyrosine kinases. Kinase activity is regulated by a 3-tyrosine motif (Tyr1278, Tyr1282, and Tyr1283), which is located in an intracellular tyrosine kinase domain.

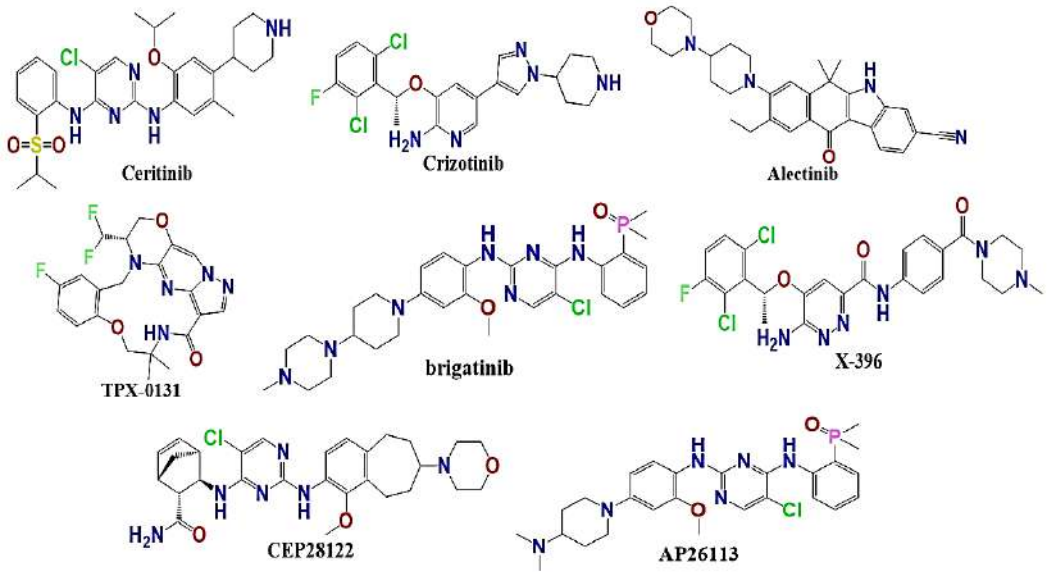


Figure 2 Some of the ALK tyrosine kinase discovered till date and available in clinical practice.

Several research studies have revealed that TKIs' ability to inhibit ALK kinase activity has a substantial anticancer effect [4-11]. Moreover, numerous potent and selective ALK-TKIs have been designed to inhibit fusion proteins and activate ALK variants[12-22]. Targeted therapy using the epidermal growth factor receptor (EGFR) has been discovered as a treatment for NSCLC patients with ALK activation mutations. However, most patients who receive targeted treatment relapse due to genetic changes that confer resistance[12,23]. Many ALK TKIs are available for cancer therapy in different regions. The FDA has approved several ALK inhibitors for cancer therapy, including ceritinib, brigatinib, crizotinib, alectinib, TPX-0131, GSK1838705, CEP28122, AP26113, and X-396 (**See fig. 2**).

In the present work, we used a QSAR-based virtual screening approach combined with drug repositioning to find a unique lead drug candidate that might effectively inhibit ALK tyrosine kinase receptors. The interactions between the newly discovered FDA drugs were investigated using molecular docking, MD modelling, and MMGBSA studies. To corroborate the results obtained virtually, we conducted an in vitro MTT experiment using the A549 lung cancer cell line.

2 Material and Method

2.1 QSAR Methodology

The current study adheres to the conventional technique advised by the OECD and other scholars for doing QSAR analysis[24-26]. All tools were used with their default values; however, certain settings were altered, and these are detailed in the documentation, in order to generate a robust QSAR model with an equilibrium of predictive capacity and mechanistic understanding.

Step 1: **Data collection and curation**:

To start, the Binding DB (https://www.bindingdb.org/bind/index.jsp; last accessed: 12/24/2021) was used to get a large dataset with 1806 IC_{50} values for experimentally proven ALK-TK inhibitors. Data quality, and suitable curation before further processing have a significant impact on QSAR analysis[25,27-29]. After that, we filtered the data[30], which included eliminating duplicates, organometallic compounds, salts, molecules with ambiguous IC_{50} values, and so on. This resulted in a reduction of the dataset's molecules from 1807 to 1328. In spite of the reduced size of the dataset, it still included molecules with experimental IC_{50} (nM) values between 0.3 and 83,000 nM and the occurrence of different scaffolds such as heterocyclic rings, positional isomers, stereoisomers, etc., all of which widened the chemical space and increased the model's applicability. Table 1 (See Table 1 in the Supplementary Materials) contains the SMILES (Simplified Molecular Input Line Entry System) nomenclature for all of the compounds used in this investigation, together with their experimental IC_{50} and pIC_{50} (=log10IC_{50}).

Table 1 shows a few representative values for IC_{50} (nM) and pIC_{50} (M) in the SMILES format, along with some examples of the most and least active compounds.

Table 1. SMILES notation, IC_{50} (nM), and pIC_{50} (M) values for the five most and least active compounds in the selected data set.

Id	SMILES	IC_{50} in nm	pIC_{50}
25	CCc1cc2C(=O)c3c([nH]c4cc(ccc34)C#N)C(C)(C)c2cc1N1CCC(CC1)N1CCC(O)CC1	0.3	9.523
33	C[C@H]1Oc2nc(cnc2N)-c2cc(ccc2CN(C)C(=O)c2ccc(F)cc12)S(C)(=O)=O	0.34	9.469
35	COc1cc(ccc1Nc1ncc(Cl)c(Nc2ccccc2P(C)(C)=O)n1)N1CCC(O)CC1	0.36	9.444
36	COc1cc(ccc1Nc1ncc(Cl)c(Nc2ccccc2P(C)(C)=O)n1)N1CCC(CC1)N1CCN(C)CC1	0.37	9.432
37	CCN1CCCc2cc(Nc3ncc(Cl)c(Nc4ccccc4S(=O)(=O)C(C)C)n3)c(OC)cc2C1	0.38	9.42
1791	CN1CCN(CC1)c1ccc(Nc2ncc3ccc(-c4ccccc4C(N)=O)n3n2)cc1	726	6.139
1793	COc1ccccc1C#Cc1ccnc2[nH]c3ccc(cc3c12)-c1ccc(cc1)N1CCN(C)CC1	750	6.125
1800	CN1CCN(Cc2ccc(cc2)C(=O)Nc2nc(cs2)-c2ccc(C)c(c2)C#Cc2ccc(C)cc2)CC1	83000	4.081
1803	CC1(C)c2[nH]c3cc(ccc3c2C(=O)c2ccc(OC[C@H](O)CO)cc12)-c1ccn[nH]1	770	6.114
1805	CC(C)S(=O)(=O)c1ccccc1Nc1nc(Nc2nc3CCN(C)CCc3s2)ncc1Cl	773	6.112

Step-2 Second, we utilised the default settings for OpenBabel 2.4[31] and MOPAC 2012 (openmopac.net, obtained on March 5, 2022) to generate SMILES notations for the optimum 3D structures of the compounds (semi-empirical PM3 technique).

Step 3: If enough molecular descriptors are generated and subsequently pruned to limit the chance of overfitting from redundant noisy descriptors, then a QSAR model may strike a satisfactory balance between mechanistic interpretation and predictive ability[32]. Then, molecular descriptors were generated from 1D to 3D for every molecule. For this objective, we used PyDescriptor [33], which can calculate over 40,000 molecular descriptors for a given

molecule. To reduce the number of molecular descriptors in the descriptor pool, we used QSARINS 2.2.4 to eliminate duplicates and variables with strong correlation (|R| > 0.95 or > 98%) [34]. This resulted in a reduction from 40,000 to 2,376, but still covered a broad spectrum of molecular descriptors.

2.2 Subjective Feature Selection (SFS) involves separating the dataset into a training set and an external set

Splitting the dataset into a training set and an external set (also known as a prediction set or test set) is essential for developing and validating a reliable QSAR model [25,27-29]. In order to exclude any possible bias, we divided the dataset into a training set of 1062 molecules (80%) and an external collection of 266 molecules (20%) for this study. The only purpose served by the external set was model validation (predictive QSAR), whereas the molecular descriptors were selected from the training set to determine how many parameters were desired. QSARINS 2.2.4 was used to develop the model through multi-linear regression (MLR) and the Genetic Algorithm (GA). With a fitness function of Q^2_{LOO} and 10,000 iterations. Determining the right number of molecular descriptors to use in a model's creation is an important step in quantitative structure-activity relationship (QSAR) modelling. Until the value of Q^2_{LOO} rose beyond a certain threshold, the heuristic search had to construct a large number of models, beginning with a univariate model and progressing to a multivariate model as additional molecular descriptors were included.

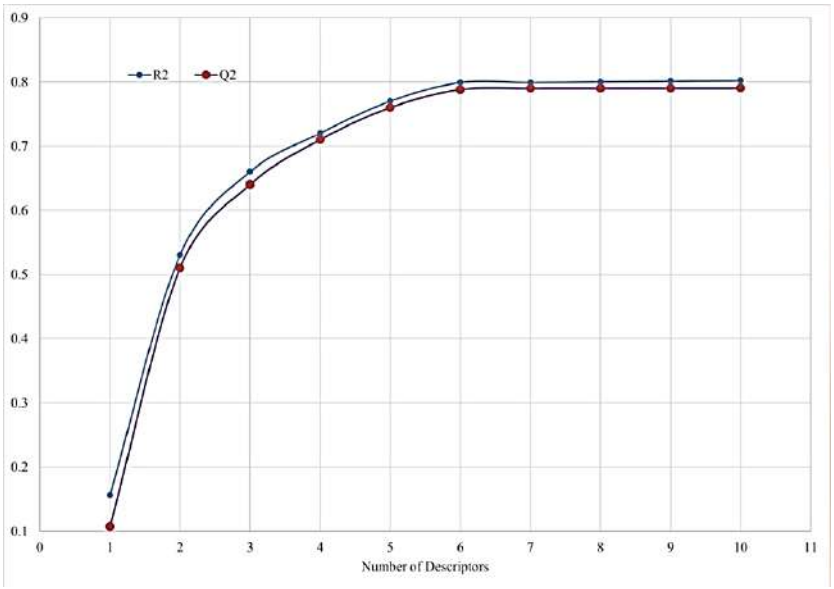


Figure 3 Graph for the number of descriptors vs. leave-one-out Coefficient. Q^2_{LOO} for optimal descriptor count.

Figure 27 is a two-dimensional graph showing the correlation between the Q^2_{LOO} values and the number of chemical descriptors employed by the models. Adding more molecular descriptors did not increase the model's statistical performance; hence, this threshold was used to determine the ideal number of variables to include in the model. The investigation established critical values for six independent variables[35,36] (**See Fig. 3**). This meant that the QSAR models with more than six descriptors had to be rejected.

2.3 Constructing a Valid Regression Model and its validation

Several validation methods, such as cross-inter validation, external validation, Y-randomization analysis, and the applicability domain (William's plot), can be used to test how

accurate and reliable a QSAR model is. A well-validated QSAR model is very helpful for virtual screening, lead/hit optimisation, decision-making, and other activities. Several types of validation—cross-inter, external, Y-randomization, and applicability domain (William's plot)—can be used to approximate the robustness and wide application of a QSAR model[25,37-40].

The following are the typical criteria for assessing QSAR models, together with their corresponding threshold values for validation parameters[35,36].There have been several successful model generation efforts using GA-MLR. The best possible model was selected using the following stringent parameters and criteria: $R^2_{tr} \geq 0.6$, $Q^2_{loo} \geq 0.5$, $Q^2_{LMO} \geq 0.6$, $R^2 > Q^2$, $R^2ex \geq 0.6$, RMSEtr < RMSEcv, $K \geq 0.05$, $CCC \geq 0.80$, Q^2-Fn ≥ 0.60, $r^2m \geq 0.5$, $(1-r2/ro2) < 0.1$, $0.9 \leq k \leq 1.1$, or $(1-r2/r'o2) < 0.1$, $0.9 \leq k' \leq 1.1$,| ro2-r'o2|< 0.3, RMSEex, MAEex, R^2ex, Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, and low R^2_{Yscr}, RMSE and MAE.

Validation of quantitative structure-activity relationship (QSAR) models entails establishing the model's applicability. We used a Williams plot to determine the extent to which the QSAR model was reliable. (Table 2 in the supplemental materials lists the computed descriptors used to create the QSAR model.) Table 3 of the supplementary materials provides the formulas for determining these statistical features.

2.4 QSAR-Based Virtual Screening for Drug Repositioning (Repurposing)

Due to the rising need for novel anticancer treatments, drug repurposing has fascinated the cancer research community. Even though there are many ways to treat cancer, such as chemotherapy and targeted therapies, cancer is defined by its inability to respond to current medicines and drugs. Because of this, studying potential novel cancer treatments is a thriving field of study[41-43]. Nowadays, drug repositioning is an emerging area of study; therefore, we utilised this information to conduct a QSAR-based virtual screening using the zinc database and its 1615 FDA compounds. Since then, QSAR-based VS has used 1615 FDA substances. Before doing molecular descriptor calculations, the 3D structures of molecules were constructed in the same way as a modelling set. The ALK-TK inhibitory action of 1615 FDA-approved drugs was predicted using a completely validated six-parameter quantitative structure-activity relationship (QSAR) model, which was derived using estimated chemical descriptors. The chemical details and predicted IC_{50} values for the zinc FDA 1615 compounds are included in Table 4 of the supplemental materials.

2.5 Molecular Docking Analysis

The ALK TK wild type (pdb-4cmu) and mutant (pdb-4clj) Protein Data Bank (pdb) data were obtained from the protein data bank[44]. The pdb:4cmu and 4clj were chosen on the basis of X-ray resolution and completion of amino acid sequences. Ramachandran's plot was used to determine the protein's health before running docking simulations. The protein, after optimisation, passes muster for docking studies. Both PDB files had their native ligands removed before docking analysis could begin. To facilitate comparison between the wild-type (4cmj) and mutant (4clj) strains, all 12 hit molecules from the QSAR-based virtual screening were docked into the active sites of both. For convenience, we've included the docking position of Ledipasvir, the most active molecule.

Molecular docking analysis was performed in NRGSuite software package [45]. This is an open-access tool that is available at no cost as a plugin for the PyMOL software (www.pymol.org as of March 9, 2022). FlexAID can help you find cavities on protein surfaces to ensure that it can be utilised in docking simulation targets[46]. Covalent docking, conformational search using a genetic algorithm, and the mobility of ligands and side chains are all modelled. For optimal performance in this study, NRGsuite was run with the following flexible-rigid docking with default parameters: Input Method for Boundary Sites: HET groups

contain water molecules; have a van der Waals permeability of 0.1; have gone through 1000 generations; use the share fitness metric; reproduce using the population explosion model; have five TOP complexes; have a cylindrical form (diameter: 19); have a three-dimensional grid spacing of 0.367; have no side-chain mobility; be ligand-adaptable; not have a ligand posture for comparison; have no constraints; and so on. For both the wild-type and mutant strains, the accuracy of molecular docking was tested using two molecules: PF-06463922 and (10R) -7-amino-12-fluoro-1, 3, 10, 16-tetramethyl-16, 17-dihydro-1H-8, 4-(metheno) pyrazole (4, 3-) (2, 5, 11). ((10R) -7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16-tetrahydro-2H-8) 4-(metheno) pyrazole (4, 3-h) (2,5,11) is a well-characterised inhibitor of ALK TK that was used to verify the docking method.

2.6 Molecular dynamics (MD) simulations

Molecular dynamics and simulation (MDS) methods were used to look into how stable and convergent the interaction between ledipasvir and ALK TK was. This study examined both wild (pdb-4cmu) and mutant (pdb-4clj) strains for their stability. The system builder was used to construct intricate systems for the strains of Ledipasvir-wild, Ledipasvir-mutant, Ceritinib-wild, and Ceritinib-mutant. This action was undertaken in order to facilitate the execution of simulations. The system used the OPLS-2005 force field and included an explicit solvent model using SPC water molecules[47,48]. The baseline parameters for the explicit SPC water model's orthorhombic box measuring 7.0 x 7.0 x 7.0 metres were established using Desmond 2018-4[49]. The neutralisation of both wild-type and mutant ALK-TK complexes was achieved by introducing NaCl salt at a concentration of 0.15 M Na+ ions. In the Desmond system builder panel, the neutralise option has been selected to introduce a predetermined quantity of counterions. In the molecular dynamics simulation approach, 18 sodium (NA) ions and 15 chloride (Cl) ions were included. After using the ASL module to choose certain residues of the ligand and protein molecules, the Desmond default relaxation technique was employed to improve the performance of the resulting systems. To learn more about each complex, we conducted molecular dynamics (MD) simulations. In the previous production run, we kept the temperature and pressure (NPT) constant and ran a molecular dynamics simulation (MDS) for 200 ns. The Nosé-Hoover chain coupling method was used to create the NPT ensemble, and the final simulation was run at 300 K with a relaxation period of 1 ps throughout the whole dynamics [49,50]. With a relaxation time of just 2 picoseconds[51], pressure was controlled using a barostat based on the Martyna Tuckerman-Klein chain coupling system. The Desmond simulation used the isotropic Martyna-Tobias-Klein barostat and the Nose-Hoover thermostat to regulate the pressure at 1 atmosphere and the temperature at 300 Kelvin. The NPT ensemble was used in all runs, with a temperature of 300 K and a pressure of 1 bar. We successfully estimated the bonding interactions by utilising a time step of 2 femtoseconds and the RESPA integrator. Using the particle mesh Ewald method, and keeping the radius for Coulomb interactions at 9 [52], we were able to calculate the long-range electrostatic interactions between the particles. This investigation describes the remaining possible setups. After finishing the last simulation run, the simulated trajectories of the wild-type and mutant Ledipasvir strains were analysed. Root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and hydrogen-bond formation were the primary areas of study in this examination. Binding energies for the complexes were estimated using the MM-GBSA technique, which was applied to 200 individual 1 ns trajectories. Standard deviations and mean binding energies were calculated from the data so obtained.

2.7 Molecular Mechanics: Generalised Borne Surface Area

Docked complexes of ledipasvir and ceritinib were analysed to determine their binding free energy (Gbind) with the help of the MM-GBSA module. During molecular dynamics (MD) simulations, the ALK complex was attached to both natural (4cmu) and mutant (4clj) strains,

allowing for this estimate to be made. The New York-based Schrodinger Suite, LLC, version 2023–24, was used to run the simulations. Binding free energy was determined using a rotamer search and calculated with the OPLS 2005 force field and the VSGB solvent model [53]. After an MD experiment was completed, a time window of 10 ns was used to choose the frames of the trajectories. By using Equation 1, the comprehensive free energy of binding was successfully determined.

$$\Delta Gbind = Gcomplex - (Gprotein + Gligand) \quad (1)$$

Where,
ΔGbind = binding free energy,
Gcomplex = free energy of the complex,
Gprotein = free energy of the target protein,
and Gligand = free energy of the ligand.
The trajectories of the MMGBSA results were analysed to learn more about the structural changes that occurred after the dynamics were applied.

2.8 In-Vitro Evaluation of Anticancer Activity by MTT Assay

The A549 lung cancer cell line, at passage 68, was purchased from NCCS, Pune, India. F-12K medium, antibiotic-antimycotic solution, HEPES solution, and 10% foetal bovine serum were used to cultivate the cells after they were frozen. The experiment used the 3(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay to assess mitochondrial function. This assay relies on the reducing properties of MTT, which lead to the formation of insoluble formazan crystals specifically inside viable mitochondria**.** In summary, 1x104 A549 cells were seeded into each well of a 96-well plate, and the plate was then incubated for 24 hours at 37°C in 5% CO2. Following removal of the medium, the cells were treated with Ceritinib (5 M), Posaconazole (10 M), Ledipasvir (20 M), and Ledipasvir (40 M) for 24 hours in triplicate. The chemical ceritinib was used as a standard. Each well was given a media volume of 300 l. After 24 hours of treatment, 25 L of MTT solution (5 mg/mL) was added to each well, and the cells were incubated for 4 hours at 37°C in a 5% CO2 atmosphere. Following the dissolution of the formazan crystals in a volume of 100 litres of dimethyl sulfoxide (DMSO), the absorbance was then determined at a wavelength of 570 nanometers using an Epoch Microplate Spectrophotometer manufactured by Biotek Instrument. The IC_{50} values were calculated using GraphPad Prism (version 7) software. Examining a nonlinear plot of the percentage of cell inhibition against the logarithm of concentration enabled this. The calculation of cell growth inhibition percentage was performed using the below formula**:**

$$\% \text{ Cell Viability} = (AT / AU) \text{ X } 100$$

Where; AT = Absorbance of Treated Cells (Drug)
AU = Absorbance of Untreated Cells, % Cell Inhibition = 100 - % Cell Viability

3 Results and Discussion

This work used molecular docking and quantitative structure-activity relationship analysis to identify ALK-TK inhibitory structural components. A QSAR paradigm combines structural characteristics to basic chemical descriptors. The six-parametric GA-MLR model's structural interpretation and clear molecular descriptors make it a good external predictor. IC_{50} values of molecules in the dataset can explain the effect of a specific descriptor, but the combined or

inverse effect of unknown factors or other molecular descriptors could have a significant impact on a molecule's IC_{50} value (**See figure 4**).

QSAR Model

$_{P}IC_{50}$= 5.577 (± 0.087) + 1.21 (± 0.102) * **aroC_sumpc** + 0.086 (± 0.006) * **ringC_plaN_6B** + 0.221 (± 0.029) ***** **fnotringNsp3C4B** + -0.269 (± 0.027) * **faroNC8B** + 1.059 (± 0.103) * **fdonnotringN5B** + -0.595 (± 0.061) * **fnotringNringN4B+**

R^2:0.7909, R^2adj:0.7897, R^2-R^2_{adj}:0.0012, LOF:0.2544, Kxx: 0.3058, Delta K:0.0661, RMSEtr: 0.4987, MAE_{tr}: 0.4215, RSStr: 264.3315, CCC_{tr}: 0.8832, s: 0.5003, F: 665.6663, Q^2_{loo}: 0.7882, R^2-Q^2_{loo}: 0.0027, $RMSE_{cv}$: 0.5019, MAE_{cv}: 0.4242, $PRESS_{cv}$: 267.7734, CCCcv: 0.8817, Q^2_{LMO}: 0.7885 ,R^2_{Yscr}:0.0056, Q^2_{Yscr}:-0.0076, $RMSEAV_{Yscr}$:1.0874, $RMSE_{ext}$:0.5285, MAE_{ext}:0.4460, $PRESS_{ext}$:74.0260, R^2_{ext}:0.7710, Q^2-$_{F1}$:0.7708, Q^2-$_{F2}$:0.7690, Q^2-$_{F3}$:0.7651, CCC_{ext}:0.8739, r^2m aver.:0.6744, r^2m delta:0.1472, R^2: 0.7882, R'^{2}o: 0.7334, k': 0.9956, Clos': 0.0695, r'^{2}m: 0.6038. Pred(x) vs. Exp(y): R^2: 0.7882, R^2o: 0.7882, k: 1.0000, Clos: 0.0000, r^2m: 0.7869, Exp(x) vs. Pred(y): R^2: 0.7710, R'^{2}o: 0.7223, k': 0.9998, Clos': 0.0632, r'^{2}m: 0.6008, R^2: 0.7710, R^2o: 0.7701, k: 0.9951, Clos: 0.0012, r^2m: 0.7480.

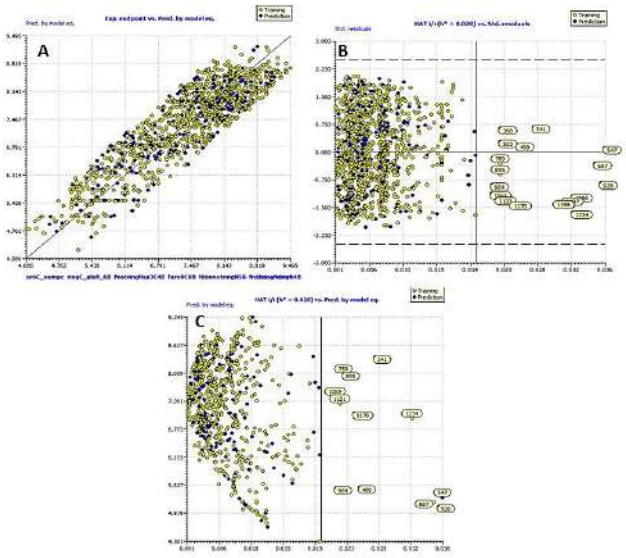


Figure 4 QSAR model development and accompanying graphs (a) A scatter plot contrasting the expected and experimental $_{P}IC_{50}$ values (b) a portrayal of a Williams plot to assess the model's applicability domain; and (c) a presentation of an Insubria plot.

3.1 QSAR Mechanistic Interpretation

The significance of the sum of partly charged carbon atoms in aromatic fragments is shown by **aroC_sumpc**. It is one of the variables that exhibit a positive correlation in the constructed QSAR model. These descriptions highlight the charges, both complete and partial, that are linked to carbon atoms with aromatic and fragrant properties. The presence of a positive coefficient for this descriptor suggests that there is a direct relationship between a greater activity profile and a higher aroC_sumpc score. The evaluation involves analysing the following pair of molecules: 502 (502, IC_{50}=4.67 nM, aroC_sumpc=0.65, ringCplus_sumpc=0.97) and 1030 (1030, IC_{50}=19.05 nM, aroC_sumpc=0.49, ringCplus_sumpc=0.85)(**see fig 5**).

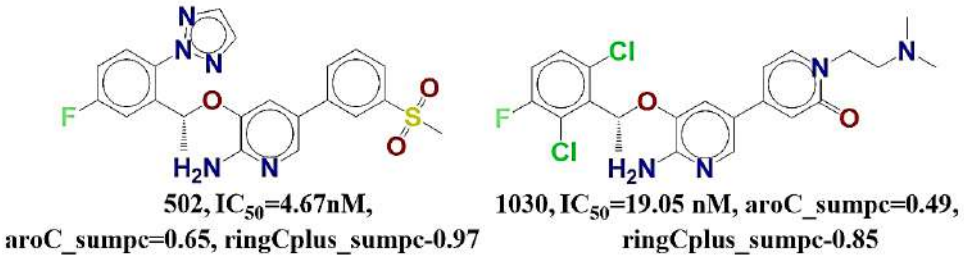


Figure 5 The molecular descriptor aroC_sumpc, shown exclusively for molecules 502 and 1030.

Ring carbon and planar nitrogen were found to be important for TK ALK to work as an inhibitor (**ringC_plaN_6B**). It shows that there are ring carbons in the six bonds of the flat nitrogen atoms. It's much better for TK-ALK to stop a reaction when the positive factor number for this trait in the QSAR model goes up. One way to show this is to compare molecule 1065 (1065, IC_{50} = 21.38 nM, ringC_plaN_6B = 20, C_plaN_5B = 26, aroC_plaN_6B = 16) to molecule 1778 (1778, IC_{50} = 69183 nM, ringC_plaN_6B = 16, C_plaN_5B = 16, aroC_plaN_6B = 12) (**See Fig. 6**)

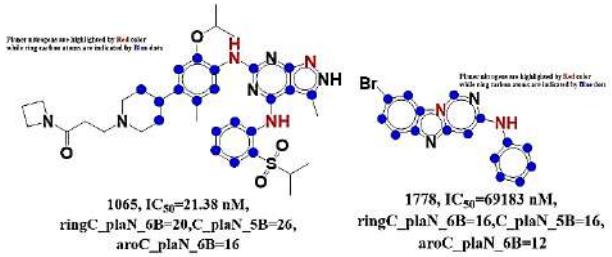


Figure 6. For molecules 1065 and 1778, the molecular descriptor ringC_plaN_6B is shown.

fnotringNsp3C4B: The abbreviation fnotringNsp3C4B describes how often Sp3-hybridized carbon atoms are found within 4 bonds of acyclic or non-ring nitrogen atoms. Since it has a positive coefficient, the value of the molecular marker fnotringNsp3C4B goes up as the activity profile does. The fnotringNsp3C4B is not worked out if the same sp3 hybrid carbon atom is three or five bonds away from the carbon atom. This is clear when you look at the molecule 135 (IC_{50} = 1 nM, fnotringNsp3C4B = 2, fnotringNnotringC4B = 2, fplaNsp3C4B = 2) next to the molecule 1670 (IC_{50} = 371.5 nM, fnotringNsp3C4B = 1, fnotringNnotringC4B = 1, fplaNsp3C4B = 1) (**See fig. 7**).

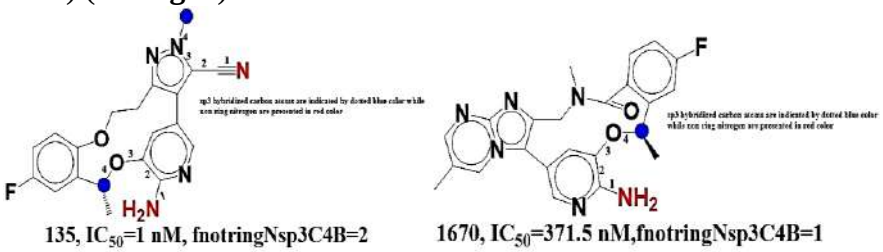


Figure 7: For molecules 135 and 1670, the fnotringNsp3C4B molecular descriptor is shown.
fdonnotringN5B (The chance of a nitrogen atom that is not in a ring is exactly 5 bonds away from the source atoms.) This trait has a positive coefficient in the standard QSAR model. This means that as its value goes up, ALK-TK suppression goes up as well. It can be seen that between molecules 245 (IC50 = 2.13 nM, fdonnotringN5B = 1) and 1449 (IC50 = 812.8 nM, fdonnotringN5B = 0). This might explain the differences in inhibitory activity of ALK TKs (**See Figure 8**).

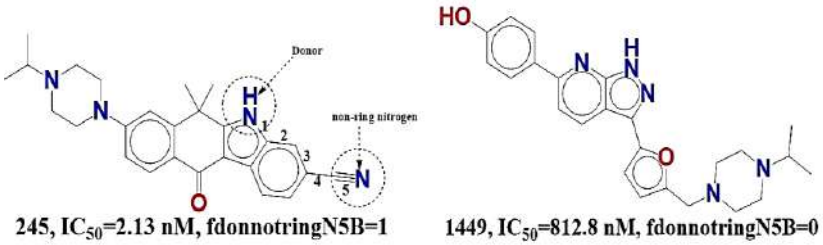


Figure 8 For molecules 245 and 1449, the molecular descriptor fdonnotringN5B is shown.

The abbreviation **faroNC8B** shows how often aromatic nitrogen atoms with carbon atoms connected in exactly 8 bonds are found. The suggested QSAR model shows that this trait has a negative coefficient. Increasing its value would make ALK TK even less effective at blocking it. To make ALK TK as good at stopping cell growth as possible, more changes should be made to the molecule that lower the value of faroNC8B. This remark can be explained by comparing molecule 1168 (IC_{50} = 107.1 nM, faroNC8B = 2) to molecule 1118 (IC_{50} = 81.8 nM, faroNC8B =1) (**see fig. 9**).

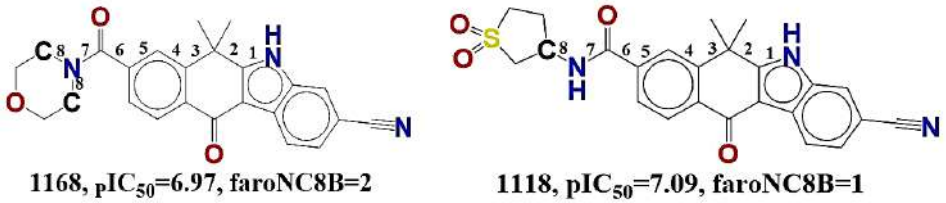


Figure 9 Illustration of the molecular descriptor faroNC8B for the molecules 1168 and 1118.

fnotringNringN4B (frequency of occurrence of a ring nitrogen atom exactly at 4 bonds from a non-ring nitrogen atom) As the value of the descriptor goes up in the QSAR model that was made, negative coefficients of the descriptor make the inhibitor less active. This can be demonstrated by comparing molecule 192 (pIC_{50} = 8.77, fnotringNringN4B = 0) with molecule 1343 (pIC_{50} = 6.43, fnotringNringN4B = 1) (**see fig. 10**).

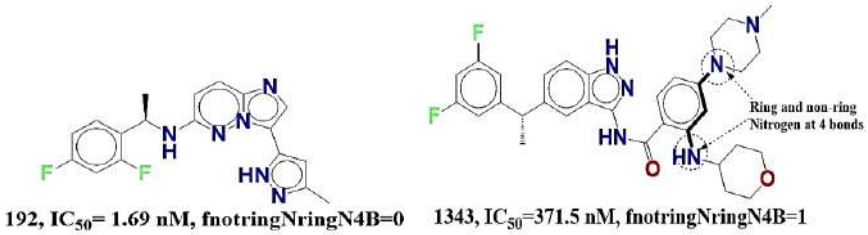


Figure 10 The fnotringNringN4B molecular descriptor is presented only for molecules 192 and 1343.

3.2 Drug Repositioning and QSAR Based Virtual Screening

After making the QSAR model, we used it to predict the ALK-TK inhibitory activity of 1650 FDA molecules through a QSAR-based virtual screening. The 12 hit molecules were obtained as repurposed drug candidates against the ALK-TK receptor. Based on its pIC_{50}, the molecule ZINC000150338819 (Ledipasvir) was chosen as a major hit among the top hit molecules.

3.4 Applicability domain study of the Identified hit molecules

To see how widely our QSAR model could be used, we used a collection of 1329 molecules for training and a set of 12 hit molecules for forecast. Twelve molecules were found through QSAR-based virtual screening and were then described. As you can see in **Fig. 11**, the hit molecules ZINC000150338819, ZINC000150588351, ZINC000203686879, and

ZINC000068204830 are on the edge of the application domain in the Williams plot. This means that the leverage value is low.

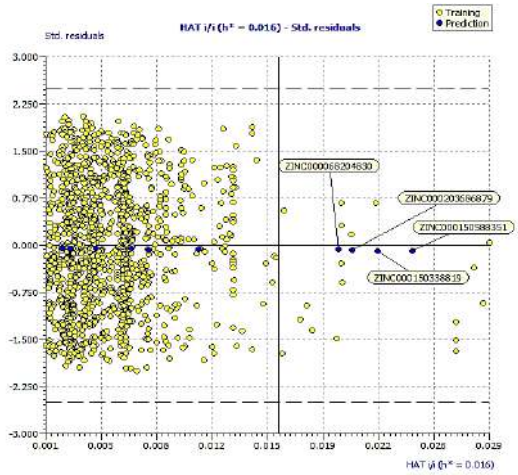


Figure 11 The 12 hit molecules from the QSAR-based virtual screening are shown in a Williams plot for their potential applicability domain (blue dots represent the hit molecules).

3.5 Molecular Docking analysis

All reported hit compounds were docked to ALK TK wild (pdb-4cum wt) and mutant strains (pdb-4clj mutant) to analyse the binding relationships. The QSAR-based virtual screening anticipated several FDA compounds' ALK-TK inhibitory activity. The docking scores and predicted activity (PIC50) of the 12 hit molecules for the wild-type ALK TK and the mutant L1196M TK are shown in Tables 1 and 2, respectively. The QSAR-based virtual screening showed that all antiviral drugs had a greater $_{P}IC_{50}$ against both wild and mutant ALK TK strains than the clinically proven ALK TK inhibitors (**See Tables 2 and 3**).

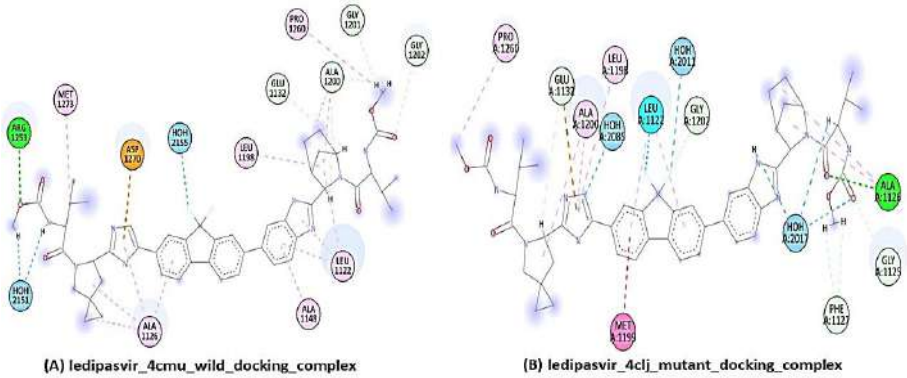


Figure 12 Depiction of 2D interaction) of ZINC000150338819 (Ledipasvir) with ALK TK wild strain (A) and mutant strain(B).

Table 2 Depiction of the Docking Results of the 12 hits for ALK TK (pdb-4cmu, wild strain)

SN	ZINC I.D. hit molecules	$_{P}IC_{50}$ by QSAR VS	Docking Score kcal/mol	RMSD Å	Binding free energy
1	ZINC000150338755 (Venetoclax)	9.36	-9.90	1.64	-38.63
2	ZINC000150338819(Ledipasvir)	9.18	-10.57	1.54	-55.19
3	ZINC000150588351(Elbasvir)	9.02	-9.93	2.37	-61.26
4	ZINC000066166864 (Alectinib)	8.67	-7.65	1.96	-34.99
5	ZINC000203686879 (Velpatasvir)	8.58	-10.08	2.10	-51.97

6	ZINC000148723177(Brigatinib)	8.53	-8.45	1.78	-29.96
7	ZINC000096272772(Ceritinib)	8.28	-8.17	1.58	-38.64
8	ZINC000028639340	8.25	-8.94	2.65	-50.07
9	ZINC000003938482(Posaconazole)	8.25	-9.70	1.59	-49.49
10	ZINC000072316335(Ribociclib)	8.20	-7.48	1.12	-34.62
11	ZINC000068204830(Daclatasvir)	8.14	-10.10	2.15	-49.15
12	ZINC000003787097(Besifloxacin)	8.03	-7.10	0.99	-32.95

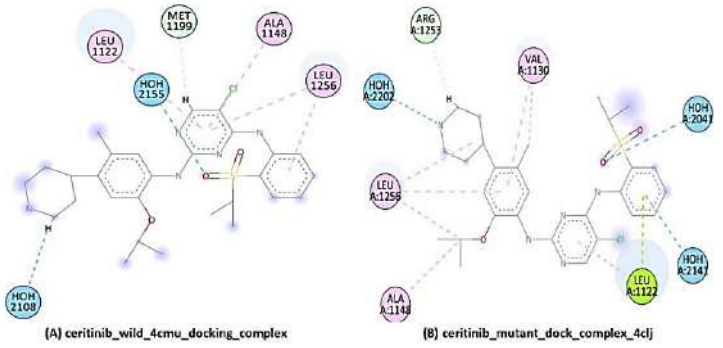


Figure 13 Depiction of 2D interaction) of ZINC000096272772 (Ceritinib) with ALK TK wild strain (A) and mutant strain(B).

Table 3 Depiction of the docking Results of 12 hits for ALK TK (pdb-4clj, mutant strain).

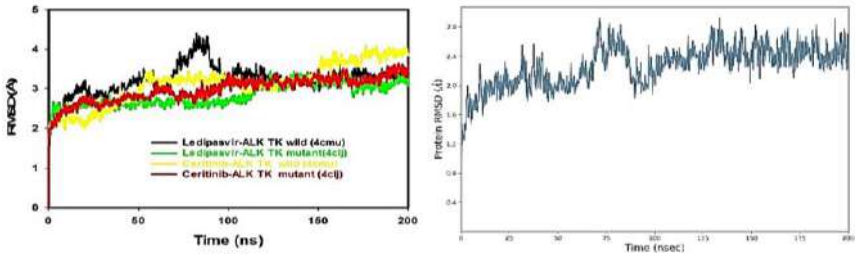
sn	ZINC I.D.	$_pIC_{50}$ by QSAR VS	Docking Score kcal/mol	RMSD A0	Binding free energy
1	ZINC000150338755 (Venetoclax)	9.36	-8.87	2.28	-46.77
2	ZINC000150338819(Ledipasvir)	9.18	-8.52	2.09	-37.33
3	ZINC000150588351(Elbasvir)	9.02	-8.95	4.25	-39.68
4	ZINC000066166864 (Alectinib)	8.67	-7.70	1.47	-32.47
5	ZINC000203686879 (Velpatasvir)	8.58	-9.35	1.70	-31.60
6	ZINC000148723177(Brigatinib)	8.53	-8.33	1.70	-40.17
7	ZINC000096272772(Ceritinib)	8.28	-8.36	1.60	-34.64
8	ZINC000028639340	8.25	-7.07	2.19	-23.41
9	ZINC000003938482(Posaconazole)	8.25	-8.29	3.46	-44.94
10	ZINC000072316335(Ribociclib)	8.20	-7.93	3.70	-39.19
11	ZINC000068204830(Daclatasvir)	8.14	-8.43	4.77	-41.96
12	ZINC000003787097(Besifloxacin)	8.03	-7.27	1.89	-30.17

It has a strong preference for Ledipasvir because the ALK TK mutant strain reacts with it in a way that is less water-friendly than the normal ALK TK. Arg1253 formed a normal hydrogen bond with Ledipasvir, and water formed hydrogen bonds with HOH2151, HOH2155, and HOH2151. It takes -0.33 kcal/mol of energy for ledipasvir to bind to Met1199 in the active "DFG-in" shape of wild-type ALK TK. It needs -0.88 kcal/mol in the mutant strain. This shows that Ledipasvir has a stronger attraction for the mutant ALK TK strain compared to the wild strain, even though the contact distance between the two strains was only 3.88. The gap between Gly1202 and fluorine atoms that made touch was found to be 4.14. In the wild ALK TK, which was shaped like a boat, no similar contact was found between Gly1202 and fluorine atoms. Also, the way the fluorine atoms are arranged in the hydrophobic pocket brings them

closer to the Asn1254 residue of the mutant ALK-TK. This improves the interactions between molecules and keeps its chair-shaped shape. Along the same lines, this is like how fluorine atoms are oriented towards the Asn1254 residue of the pdb-4clj binding. The difference in binding free energy between the two strains could be because Ledipasvir has different shapes when it comes to normal and mutant ALK TK. Also, the wild ALK TK had a fluorine atom arrangement with a dihedral angle of 52.2 degrees. The mutant ALK TK, on the other hand, had an angle of 70 degrees, which means it rotated 18 degrees differently. This shows that the mutant ALK TK goes through big changes in its shape that affect its capacity to attach to Ledipasvir (see **fig 112 and 13**).

3.6 Molecular dynamics (MD) simulations

The apo-ALK tyrosine kinase (TK) was stable throughout the 200-nanosecond simulation, except for a 60–85 nanosecond variation. The c-alpha atoms' root mean square deviation (RMSD) varied from 2.0 to 2.2 angstroms at this time. The system converged at 2.27 angstroms RMSD. The apo-ALK tyrosine kinase (TK) showed larger variations in the back area (RMSD = 2.3 Å) and sidechain region compared to the C- and backbone regions (RMSD = 3.2) (see figure 1(B)). Figure 1 indicates that the wild type A-loop RMSD converged to 1.8 after 40 ns of simulation. In the L1196 mutant, the A-loop RMSD reached 2.4 at 40 ns and varied between 40 and 50 ns. The value dropped to 2.4 between 100 and 110 ns after reaching 3.1 between 80 and 90 ns. The MD simulation ended with it rising from 2.6 to 2.8. This suggests that the L1196 mutant's A-loop is more flexible than the normal type (**see fig. 14**).



(A) **(B)**

Figure 14. (**A**) Root Mean Square Deviation (RMSD) analysis of MD simulation trajectories for (i) wild (4cmu) Ledipasvir-ALK TK, (ii) mutant (green, yellow) (4clj) Ledipasvir-ALK TK, (iii) wild (4cmu) Ceritinib-ALK TK, and (iv) mutant (red, 4clj) Ceritinib-ALK TK. (**B**) RMSD plot for the Apo-4cmu (non-complex) ALK TK protein.

Figure 19 demonstrates that the wild type A-loop RMSD converged to 1.8 after 40 ns of simulation. The A-loop RMSD of the L1196 mutant increased to 2.4 at 40 ns and ranged from 40 to 50 ns. Between 80 and 90 ns, it hit 3.1 before dropping to 2.4 between 100 and 110 ns. Later in the MD simulation, it rose from 2.6 to 2.8. The L1196 mutant's A-loop is more flexible than the normal kind.

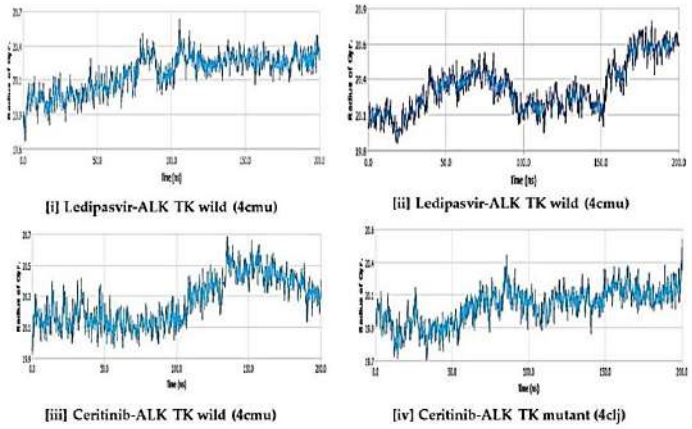
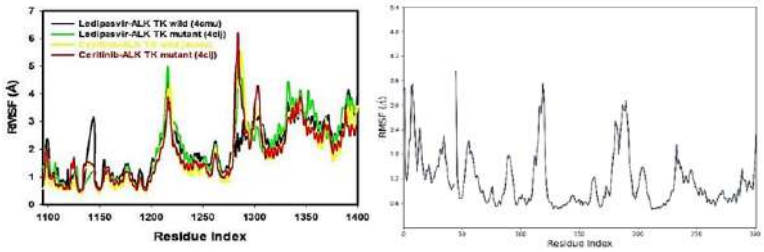


Figure 15. Radius of gyration (Rg) trajectory study using MD simulations for [i] wild (4cmu) and [ii] mutant (4clj) Ledipasvir-ALK TK, [iii] wild (4cmu) and [iv] mutant (4clj) Ceritinib-ALK TK.

In **figure 15**, the C-backbone of ALK TK wild-type coupled to Ledipasvir has the least compactness because its Rg plot fluctuates from 20.1 to 20.7, with a mean of 20,3 over 200 ns. However, the C backbone of the ALK-TK mutant bound to Ledipasvir gyrated at 8.5 with minor modifications. A reduction in Rg indicates a well-bound protein-ligand combination. Mutant ALK-TK complexes with Ledipasvir were substantially more stable than wild-type ones. Throughout the simulation, the RMSF plot showed each amino acid residue in its most stable configuration. The amino acid residues in the ledipasvir-bound wild-type and mutant ALK TK complex were least likely to alter (**see fig. 16**).



(A) **(B)**

Figure 16. **(A)** Root Mean Square Fluctuations (RMSF) in MD simulations of [i] wild (4cmu) and [ii] mutant (4clj) Ledipasvir-ALK TK, [iii] wild (4cmu) and [iv] mutant (4clj) Ceritinib-ALK TK. **(B)** Root Mean Square Fluctuations (RMSF) in MD simulations of Apo-ALK TK (non-complexed ALK TK).

Global quality study of RMSD and Rg demonstrates that ledipasvir significantly affects the stability of wild-type and mutant ALK TK targets in the binding cavities. Root mean square fluctuation (RMSF) plots with a time function of 200 nanoseconds indicated considerable RMSF at particular residues in both wild-type and mutant ALK-TK proteins. In contrast, apo-ALK TK fluctuated less.

3.7 Molecular Mechanics Generalised Born Surface Area (MMGBSA)

MMGBSA is mostly used to measure ligand-protein binding. Ledipasvir-ALK TK wild-type (4cmu) and mutant (4clj) complexes' binding free energies, ceritinib-ALK TK complexes' binding free energies, and other non-bonded interaction energies were assessed. The Ledipasvir ligand bound to the wild-type (4cmu) and mutant (4clj) ALK TK complexes at -47.77 and -61.68 kcal/mol, respectively. Table 5 shows the average binding energies of the wild-type (4cmu) and mutant (4clj) ceritinib-ALK TK complexes, -58.49 and -51.31 kcal/mol. Unlike

ceritinib, ledipasvir bound to mutant ALK TK more strongly than native ALK TK. Gbind is governed by non-covalent interactions such GbindCoulomb, GbindCovalent, GbindHbond, GbindLipo, GbindSolvGB, and GbindvdW. GbindLipo and GbindCoulomb contributed less energy than GbindvdW, but all three energies affected the binding affinity between wild-type and mutant ALK TK and ceritinib. A key role for GbindvdW in drug receptor interactions has been discovered. In contrast, GbindSolvGB and Gbind covalent energies had the least effect on mean binding energies (see **table 4**).

Table 4 Presentation of the MMGBSA results for the ledipasvir and ceritinib wild and mutant ALK TK strains.

Energies (kcal/mol) *	Ledipasvir-ALK-TK wild (4cmu)	Ledipasvir-ALK-TK mutant(4clj)	Ceritinib-ALK-TK wild (4cmu)	Ceritinib-ALK TK-mutant (4clj)
ΔGbind	-47.77 ± 6.95	-61.68±8.16	-58.49±4.42	-51.31±6.29
ΔGbindLipo	-17.98 ± 1.95	-22.92±2.55	-19.20±1.46	-17.51±2.01
ΔGbindvdW	-52.58 ± 6.71	-66.37±5.71	-54.49±3.75	-54.21±5.77
ΔGbindCoulomb	-17.51± 15.17	9.10±13.51	10.96±10.63	11.57±3.17
ΔGbindHbond	-0.85 ± 0.47	-0.93±0.53	-0.95±0.50	-0.60±0.35
ΔGbindSolvGB	9.98 ± 13.37	14.32±12.01	-1.40±9.36	5.82±3.12
ΔGbindCovalent	6.86 ± 3.59	5.59±2.66	6.59±3.12	3.64±2.17

The wild-type and mutant ledipasvir and ceritinib-ALK TK complexes formed stable hydrogen bonds with amino acid residues. Their GbindHbond interaction values showed this. Both GbindSolvGB and GbindCovalent showed negative energy contributions for each molecule, indicating binding resistance. Ledipasvir and ceritinib have transformed from curved to straight in the binding pockets of wild-type and mutant ALK-TK proteins (200 ns). Changes in conformation improve contact between the binding pocket and residues, increasing stability and binding energy.

3.8 MTT Assay (In-Vitro Cell line study)

Ledipasvir and posaconazole, our most active hits, were tested in vitro on A549 cell lines for anticancer activity. Ledipasvir and posaconazole were selected for in vitro cell line research because they are in or near the QSAR model's applicability region.

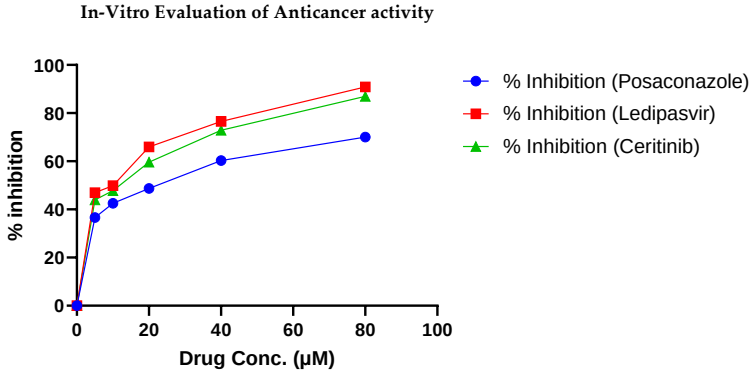


Figure 17: Depiction of in-vitro evaluation of anticancer activity.

Our study of in vitro anticancer activity on the A549 lung cancer cell line found that our acquired hit, Ledipasvir, had a slightly higher inhibition rate than the standard reference molecule, Ceritinib (**see figure 17**). The findings match computer predictions, indicating that the same mechanism that reduced A549 lung cancer cells may inhibit ALK TK. However, we believe further enzyme tests are needed to provide greater information.

4 Conclusion

A six-descriptor QSAR model was created for 1328 drugs exhibiting TK-ALK inhibitory activity (IC50). The robust and predictive QSAR model meets all threshold values, including $R^2 = 0.79$, $Q^2_{LOO} = 0.78$, $Q^2_{LMO} = 0.78$, $R^2_{ex} = 0.77$, $CCC_{ex} = 0.87$, etc. The model discovered many hidden pharmacophoric features, including the sum of aromatic carbon partial charges, sp3-hybridized carbons within 4 bonds of non-cyclic carbons, and planer nitrogen within 6 bonds of the ring carbon atom. The Quantitative Structure-action Relationship (QSAR) research showed that the aromatic or ring carbon atom, ring nitrogen atom, or non-ring nitrogen atom significantly affected ALK TK's inhibitory action. As with other TK ALK inhibitors like crizotinib and brigatinib, X-ray-resolved structures confirmed the mix of revealed and hidden structural features. Additionally, QSAR-based virtual screening and drug repositioning identified ledipasvir as an FDA-approved compound with a clinical trial IC50 of 0.65 nM ($_pIC_{50}$–9.18 M). Ledipasvir outperformed ceritinib in molecular docking, scoring -10.57 kcal/mol against the ALK TK wild strain (pdb-4cmu) and -8.5286303 against the mutant strain (pdb-4clj, mutant). Ledipasvir has a greater binding energy than ceritinib (-38.64 kcal/mol against natural ALK TK and -34.64 against mutant ALK TK) and other ALK TK inhibitors, according to docking research. Ledipasvir had a high affinity because the ALK-TK mutant strain established more hydrophobic contact with it than the natural strain. The MD simulation and MMGBSA analysis showed that the drug-receptor complex was stable beyond 200 ns and had high binding energy. The mutant ALK TK-ledipasvir combination was much more stable than the natural complex. Thus, MD simulation trajectories and binding energy docking data validated MM-GBSA predictions. Additionally, the MTT test showed that ledipasvir had somewhat stronger anticancer activity against the lung cancer cell line A549 than ceritinib. The in-silico investigation confirms the in vitro anticancer effectiveness. These results may help design a novel ALK-TK chemotherapy treatment.

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40
Synthesis, characterization and biocidal study of some novel 2-hydroxy 4,6-disubstituted phenyl pyrimidines bearing 4-bromo phenol moiety

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ABSTRACT

In the present research work a series of 2-Hydroxy 4,6-disubstituted phenyl Pyrimidine derivatives was synthesized from 4-bromo phenol as a precursor. The compound 4-bromo phenol react with acetic anhydride to obtained 4-bromo phenyl acetate (1) then it follows Fries' rearrangement reaction to form 5-bromo,2-hydroxy acetophenone(2).The compound(2) allowed to react with different benzoic acids to give corresponding substituted 2-benzoyloxy acetophenone (3a-d) which follow B.V.T. rearrangement reaction to obtained propan1,3-diones(4a-d) and then it reacts with Urea to yield 2-hydroxy 4,6-disubstituted phenyl pyrimidine derivatives (5a-d).The newly synthesized compounds are characterized by IR, H^1NMR, Mass spectral and elemental analysis. These compounds were also screened for their biocidal study i.e., antibacterial, antifungal, anti-oxidant and anti-inflammatory activities.

KEYWORDS: 4-bromo phenol, Urea,2-Hydroxy 4,6-disubstituted phenyl Pyrimidine, antibacterial, antifungal, anti-oxidant and anti-inflammatory activities.

INTRODUCTION

Heterocyclic compounds are abundant in nature and it have great significance to life. The natural heterocyclic compounds such as vitamins, hormones, antibiotics etc. These heterocyclic compounds containing nitrogen play an important role in medicinal chemistry and also contribute to the society. Pyrimidine is a six-member heterocyclic compound which contains two nitrogen atoms at positions 1 and 3. Pyrimidine derivatives are known to be biologically active compounds and substituted pyrimidines have shown wide range of biological activities like Anticancer **[1,2],** antibacterial **[3-6],** antifungal **[7]**, antioxidant **[8,9],** anti-inflammatory **[10,11],**anti-HIV **[12],**antitumor **[13]**, antiparasitic **[14]**,anti-Alzheimer's agent **[15]**, anti-diabetic agent **[16].**In addition to the diverse biological activities of pyrimidines play an essential role in several biological processes and have a considerable chemical and pharmacological importance. In the present research work some novel 2-hydroxy 4,6-disubstituted phenyl pyrimidine(5a-d) compounds have been synthesized and studies their structural characterization, antibacterial, antifungal, antioxidant and anti-inflammatory activities.

EXPERIMENTAL SECTION

Materials and Methods

All the solvents and chemicals were of research grade and highest purity. The IR spectrum was recorded by using Shimadzu IR affinity-1FTIR instrument, H^1NMR spectra were recorded on Bruker advance II 400 MHz spectrometer, Mass spectra were recorded on ESI and Melting point were determined by open capillary tube method which are uncorrected.All the synthesized compounds were purified by recrystallization and purity of the compound was checked by TLC and elemental analysis.

General procedure for the Synthesis of 2-hydroxy 4,6-disubstituted phenyl Pyrimidine derivatives (5a-d)

The synthesis involves the following steps.

Synthesis of 4-bromo phenyl acetate (1)

Take 4-bromo phenol (0.05M) fused with acetic anhydride(5ml) and sodium acetate. The mixture was refluxed for 1hr. then cooled for 15 min. and poured in ice water. Acetate layer was separate out by separating funnel. The product was obtained 4-bromo phenyl acetate (1).

Synthesis of 5-bromo,2-hydroxy acetophenone (2)

Place aluminum chloride (120 g) in kjeldal flask and add compound (1)(40 ml) drop wise. Heat the reaction mixture in oil bath for 60 min at 120^0C. It was cooled and add in to acidified ice crushed water to get crude product of 5-bromo,2-hydroxy acetophenone (2).

Synthesis of 2-substituted benzoyloxy 5-bromo acetophenone (3a-d)

A mixture of compound (2)(0.05M) and substituted benzoic acid (0.05M) were dissolved in dry pyridine at 0^0 C.Then add $POCl_3$ dropwise with constant stirring bellow 10^0C.The reaction mixture was allowed to stand for overnight at room temperature.Then it was poured in ice cold 10% HCl.Then the product was wash by 10% $NaHCO_3$ and water. Recrystallized the product by ethanol to obtained a series of 2- substituted benzoyloxy 5-bromo acetophenone (3a-d).

Synthesis of substituted propane 1,3-diones (β-diketones) (4a-d)

Take compound (3a-d) (0.05M) was dissolved in dry pyridine. The reaction mixture was heated up to 60^0C with pulverized KOH slowly with constant stirring. After 5-6 hr. the reaction mixture was acidified by dil. HCl in ice cold water. The crude product was filtered, washed it with $NaHCO_3$ (10%) and water. Recrystallized the product from ethanol-acetic acid mixture to get substituted propane 1,3-diones (4a-d).

Synthesis of 2-hydroxy-4,6-disubstituted phenyl pyrimidine derivatives (5a-d)

A mixture of compound (4a-d) (0.02 M) and urea (0.02 M) dissolved in DMF solvent. It was refluxed on water bath at 75^0C for 1hr. then mixture was cooled and pour in ice cold water. The product was recrystallized by aq. alcohol to obtained a series of 2-hydroxy-4,6-disubstituted phenyl pyrimidine derivatives (5a-d)

General reactions scheme is given bellow.

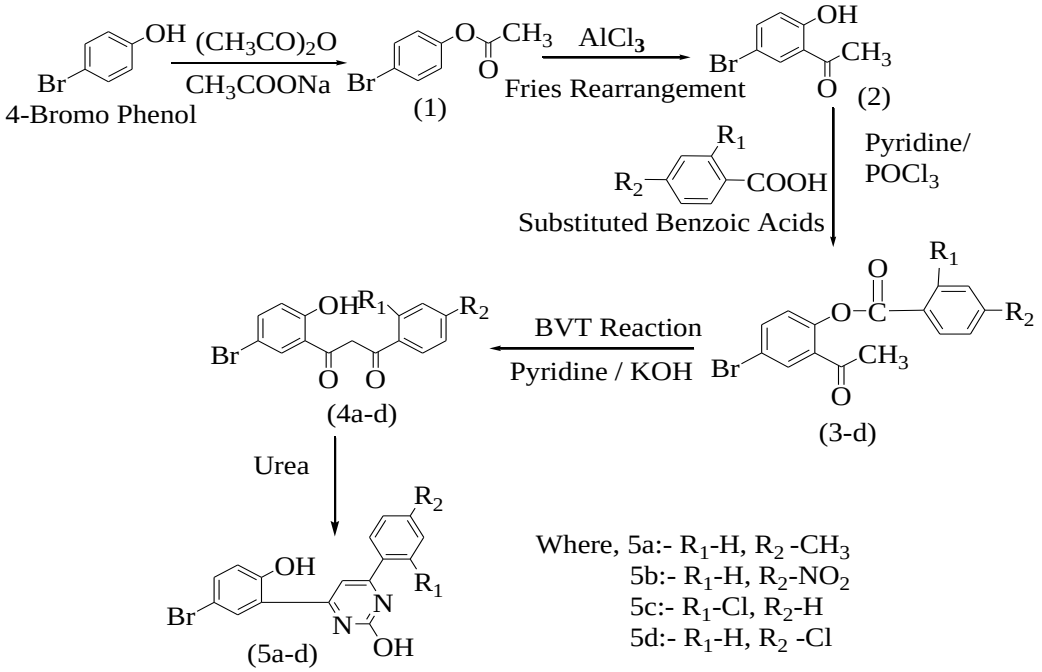


Figure-1-The general reaction scheme for the synthesis of 2-hydroxy-4,6-disubstituted phenyl pyrimidines (5a-d)

Table No.1: Physical data of 2-hydroxy-4,6-disubstituted phenyl Pyrimidines (5a-d)

Code	Compound Name	M.F./ M.W.	Rf value	M.P. (^{0}C)	Yield (%)
5a	2-hydroxy-4-(4-methyl phenyl)-6-(2-hydroxy-5 bromo phenyl) pyrimidine	$C_{17}H_{13}BrN_2O_2$ / (357.20)	0.72	80 - 86	58%
5b	2-hydroxy-4-(4-nitro phenyl)-6-(2-hydroxy-5 bromo phenyl) pyrimidine	$C_{16}H_{10}BrN_3O_4$ / (388.17)	0.68	116 - 122	71%
5c	2-hydroxy-4-(2-chloro phenyl)-6-(2-hydroxy-5 bromo phenyl) pyrimidine	$C_{16}H_{10}BrClN_2O$/ (377.96)	0.66	74 - 78	61%
5d	2-hydroxy-4-(4-chloro phenyl)-6-(2-hydroxy-5 bromo phenyl) pyrimidine	$C_{16}H_{10}BrClN_2O$/ (377.96)	0.70	112-116	65%

Antimicrobial Activity

The in-vitro anti-microbial screening of newly synthesized 2- hydroxy -4,6-disubstituted phenyl pyrimidines (5a-d) was carried out against bacteria *staphylococcus aureus (gram +ve),Salmonella typhus* (*gram–ve*) and fungi *Candida albicans and aspergillus niger* by disc diffusion method**[17**,**18]** and compared with that of the standard drugs Oxacillin (2 µg) and Fluconazole(25µg) respectively of each drug was defined as the lowest concentration of an antimicrobial that will inhibit the visible growth of microorganism after incubation time. Muller Hinton Agar was used as basal medium for test of bacteria and fungi respectively. The compounds tested at concentration of 50 µg/ml, 100 µg/ml and 250 µg/ml for bacterial and fungal growth in DMSO solvent it was added to the wells made on culture medium. After 24 hrs. of incubation at 37^{0}C for antibacterial activity and after 24 hrs. at room temp. for antifungal activity, record the zone of inhibition was compared with the standard drug Oxacillin and Fluconazole.

Anti-Inflammatory Activity

Take 10 mg of Ibuprofen as a reference drug was added to10 ml of distilled water. Serial dilution from above stock solution takes 0.1ml, 0.2ml, 0.3ml and prepare 10 ppm, 20 ppm and 30 ppm and also it was performed for sample 2- hydroxy -4,6-disubstituted phenyl pyrimidines (5a-d) extract. The reaction mixtures were prepared using 2.8 ml of phosphate-buffered saline (pH 6.4) and 0.2 ml of egg albumin. Then take 2 ml of extract from each different concentration were mixed gently with reaction mixtures. A similar procedure was used for reference drug ibuprofen. The absorbance of these solutions was determined by using spectrophotometer at wavelength of 660 nm. The % denaturation of the protein (% inhibition) was determined.**[19]**

Anti-Oxidant Activity

Stock solution of DPPH (2,2-diphenyl-1-picrylhydrazyl) was prepared by dissolving 1.083 mg in 10 ml of ethanol. Stock solution of sample 2-hydroxy-4,6-disubstituted phenyl pyrimidines (5a-d) take 100 µg/ml was prepared by dissolving 1 ml of sample in 10 ml of ethanol. From this stock solution, further dilutions were prepared of concentrations 10,20,30,40 and 50 µg/ml using ethanol.Similarly,stock solution of standard ascorbic acid was prepared by dissolving 10 mg ascorbic acid in 10 ml ethanol.From this stock solution further dilutions of concentrations 1,2,3,4 and 5µg/ml were prepared.Absorbance of blank(5 ml ethanol+1 ml DPPH solution) as a positive control was recorded using colorimeter at 517 nm.Similarly,the absorbance of

sample and comparative standard ascorbic acid was taken at 517 nm.The % scavenging activity was determined.**[20]**

RESULTS AND DISCUSSION

Spectroscopic characterization data

(5a) 2-hydroxy-4-(4-methyl phenyl)-6-(2-hydroxy-5 bromo phenyl) pyrimidine

Solid,yellow,IR(cm-^{1}):3200(Ar-OH),3058(Ar-C-H),2928(Ar-CH_3),1613(C=N),1458(C=C), 640 (C-Br),1280(C-O);^{1}H-NMR(δppm):δ7.90-7.98(m,8H of Ar-H),δ7.36-7.40 (s,1H of -OH),δ 2.38 (s,3H of -CH_3);MASS (m/z,%):358(M+); C,H,N,O% Calculated(Found) C:57.16 (56.86),H:3.67 (3.61),N:7.84 (7.62),O:8.96 (8.17).

(5b) 2-hydroxy-4-(4-nitro phenyl)-6-(2-hydroxy-5 bromo phenyl) pyrimidine

Solid, yellow, IR (cm-^{1}):3379 (Ar-OH),3096 (Ar-C-H),1605 (C=N),1456 (C=C),705 (C-Br),
1207 (C-O),1345 (-NO_2);^{1}H-NMR (δ ppm):δ7.2-8.4 (m,8H of Ar-H),δ 6.85 (s,1H of Ar-OH); MASS (m/z,%):388.99 (M+);C,H,N,O% Calculated (Found):C:49.51 (48.29),H:2.60 (2.13), N:10.83 (10.01),O:16.49 (15.59).

(5c) 2-hydroxy-4-(2-chloro phenyl)-6-(2-hydroxy-5 bromo phenyl) pyrimidine

Solid, brown, IR (cm-^{1}):3076 (Ar-OH),2927 (Ar-C-H),1637 (C=N),1459 (C=C),529 (C-Br), 1275 (C-O),757 (C-Cl);^{1}H-NMR (δ ppm): δ7.31-8.19 (m,8H of Ar-H),δ 6.69 (s,1H of Ar-OH);MASS (m/z,%):377.97(M+); C, H, N, O% Calculated (Found): C:50.89 (50.02),H:2.67 (2.13),N:7.42 (7.15),O:8.47 (7.98).

(5d) 2-hydroxy-4-(4-chloro phenyl)-6-(2-hydroxy-5 bromo phenyl) pyrimidine

Solid, yellow, IR (cm-^{1}):3188 (Ar-OH),3088 (Ar-C-H),1610 (C=N),1465 (C=C),527 (C-Br), 1274 (C-O),641 (C-Cl);^{1}H-NMR (δ ppm):δ7.90 -7.98 (m,8H of Ar-H),δ7.36 -7.40 (s,1H of Ar-OH);MASS (m/z, %):379(M+);C,H,N,O % Calculated (Found): C:50.89 (50.12),H:2.67 (1.99),N:7.42 (6.76),O:8.47 (8.17).

BIOCIDAL STUDY

Table No.2- Antibacterial activity of 2-hydroxy 4,6-disubstituted pyrimidines (5a-5d)

Compound code	Zone of inhibition in mm							
	Salmonella typhi (gram -tive)				*Staphylococcus aureus (gram +tive)*			
	Concentrations µgm/ml				Concentrations µgm/ml			
	50	100	250	Standard Ofloxacin 2 mcg	50	100	250	Standard Ofloxacin 2 mcg
5a	++	++	++	++	++	+++	+++	+++
5b	++	++	++	-	-	-	-	-
5c	-	-	-	-	++	+++	+++	-
5d	-	-	-	-	-	++	++	-
Highly active+++=13-24,Moderate active++=7-12,Less active+=1-6,No zone of inhibition-								

Table No.3- Antifungal activity of 2-hydroxy 4,6-disubstituted pyrimidines (5a-5d)

Compound code	Zone of inhibition in mm							
	Candida albicans				*Aspergillus niger*			
	Concentrations µgm/ml				Concentrations µgm/ml			
	50	100	250	Standard Fluconazole 25 µgm	50	100	250	Standard Fluconazole 25 µgm
5a	-	-	-	+++	-	-	-	+++
5b	-	-	++	-	-	++	++	-
5c	-	++	+++	-	-	-	++	-
5d	-	-	-	-	-	-	-	-
Highly active+++=13-24/Moderate active++=7-12/Less active+= 1-6/No zone of inhibition-								

The antibacterial activity results revealed that compounds showed significant activity against gram +ve organisms. The compound 5a and 5b showed moderate activity against *Salmonella typhi* and compounds 5a and 5c shows highly activity and 5d shows moderate activity against *Staphylococcus aureus*.The compounds 5c and 5d does not showed any zone of inhibition against the gram –ve organism. In the antifungal activity, compound 5b and 5c showed moderate to weak activity against *Candida albicans and Aspergillus niger*.The compounds 5a and 5d does not showed any zone of inhibition in fungal activity at different concentration.

Table No.4-Anti-inflammatory activity of 2-hydroxy 4,6-disubstituted pyrimidines(5a-d)

Sr. No.	Compound Code	% Inhibition		
		Concentration of compound in ppm		
		10 ppm	20 ppm	30 ppm
1	5a	40.67	63.68	73.06
2	5b	45.47	53.75	68.76
3	5c	6.34	17.88	59.71
4	5d	66.33	77.81	79.41
5	Ibuprofen	87.36	88.90	90.23

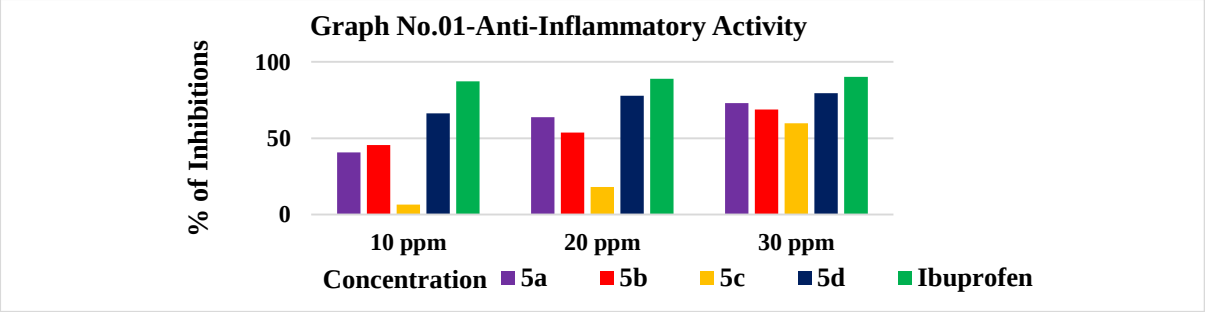
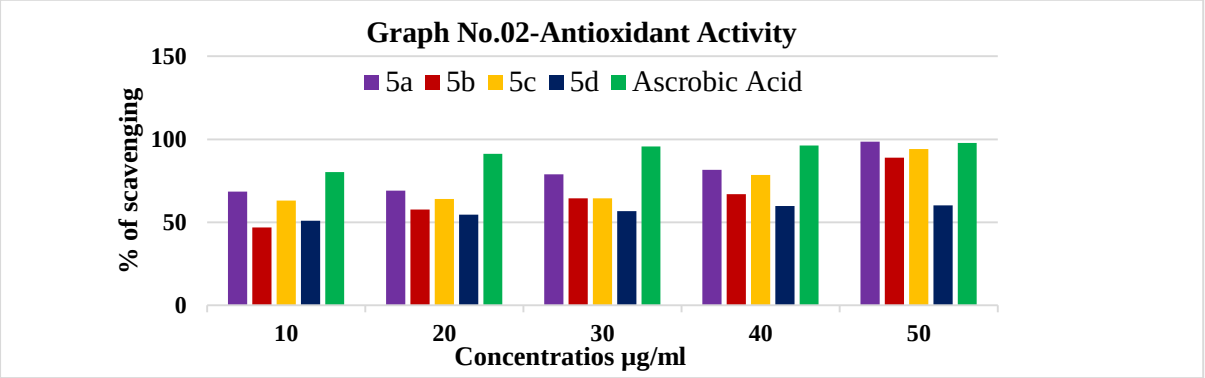


Table No.5- Anti-oxidant activity of 2-hydroxy 4,6-disubstituted pyrimidines(5a-d)

Sr. No.	Compound Code	% scavenging activity				
		Concentration of compound in µg/ml				
		10 µg/ml	20 µg/ml	30 µg/ml	40 µg/ml	50 µg/ml
1	5a	68.43	69.08	78.95	81.58	98.46
2	5b	46.93	57.68	64.48	66.89	88.82
3	5c	63.16	64.04	64.48	78.51	94.08
4	5d	50.88	54.61	56.80	59.87	60.09
5	Ascorbic Acid (Standard)	80.26	91.22	95.61	96.27	97.80



CONCLUSION

In the present work newly synthesized 2-hydroxy 4,6-disubstituted phenyl Pyrimidines containing 4-bromo phenol moiety involves different steps to get good yield. The structure of synthesized compound was elucidated on the basis of ^{1}H-NMR, IR and Mass spectra. In antibacterial activity compound 5a and 5b shows moderate activity against *Salmonella typhi* and the compound 5a,5c and 5d shows highly active to moderate zone of inhibition against *Staphylococcus aureus*. In antifungal activity compound 5b and 5c showed moderate to weak activity against *Candida albicans and Aspergillus niger* at concentration 100 µgm and 250 µgm. Also compounds **5a,5b,5c** and **5d** exhibited significant anti-inflammatory activity by using albumin denaturation technique at 30 ppm concentration. Antioxidant activity as indicated by absorbance of compounds 5a-5d increased with increasing concentration. Higher value of absorbance of the reaction mixture indicated greater reducing power. The reducing power was found to be in order of 5a>5c>5b>5d

ACKNOWLEDGEMENT

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41

Investigation of antimicrobial Activities of Dihydropyrazines

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Abstract
Seven Dihydropyrazines **4a–g** are screened for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi* and antifungal activity against *Candida albicans, Aspergillus flavus, Rhizopus* and *Mucor*. Ciprofloxacin is used for the standard for antibacterial and Amphotericin B is used for the standard for antifungal studies. Compounds **4b**, **4c,4f**and **4g**exhibited excellent *in vitro* antibacterial activity against all the tested organisms. Whereas the same set of compounds exerted potent *in vitro* antifungal activity against *Candida albicans, Aspergillus flavus* and *Rhizopus.*

Keywords: Dihydropyrazines,Antibacterial activity, antifungal activity, Ciprofloxacin, Amphotericin B.

1. INTRODUCTION

The biological and physical roles of dihydropyrazines(DHPs)such asDNA cleavage[1],growthinhibitionof*Escherichiacoli*[2],Cyclooxygenaseinhibitoryactivity [3] and NPY antagonists [4] are well documented. Dihydropyrazinesare universal in the human body[5]however, there is little reported concerning the biological and physiological roles of DHPs.Yamaguchi *etal.*[1]reported generation of free radicals from dihydropyrazineswithDNAStrand-Breakageactivity.Takechi*etal.*[6]reportedthegrowthinhibitionandmutagenesisinducedin Escherichia coli by dihydropyrazines with DNA strand-cleavingactivity.2-cyanopyrazinederivativesshowanticancerantiinflammatoryandanalgesicactivities[7].Pyrazine derivatives exits a tuberculostatic activity [8]. It also exhit a antimicrobial [9] and biological [10] activities. Alkyl substituted pyrazines are found in the growth medium of the polymyxin-producingbacterium *Paenibacilluspolymyxa*[11].

The se observations place snew emphasis on then need of as well as search for alternative new and more effective antimicrobial agents with abroad spectrum.

The aim of this study was to evaluate the biological activities of dihydropyrazines **4a–4g**. The results of the antibacterial and antifungal activities are discussed in this paper. To percept structure-activity relationship well, numberings of the target compound is shown below **Fig. 1**.

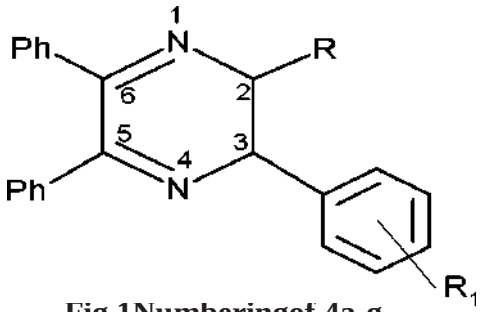


Fig.1Numberingof 4a-g

2. MATERIALS & METHODS

2.1 Materials

All the bacterial strains namely *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella typhi* and fungal strains namely *Candida albicans*, *Aspergillus flavus*, *Rhizopus* and *Mucor* were obtained

2.2 Methods

The compounds were synthesized by the following literature procedure .[12] The *in vitro* antimicrobial activities of the compounds were tested in Sabouraud's dextrose broth (SDB, Hi-media, Mumbai) for fungi and nutrient broth (NB, Hi-media, Mumbai) for bacteria by the twofold serial dilution method.[13]

The test compounds were dissolved in dimethyl sulfoxide (DMSO) to obtain 1 mg/ml stock solutions. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1 °C while fungal spores from 24 h to 7-day-old Sabouraud's agar slant cultures were suspended in SDB. The colony forming units (cfu) of the seeded broth were determined by the plating technique and adjusted in the range of 10^4–10^5 cfu/ml. The final inoculum size was 10^5 cfu/ml for the antibacterial assay and 1.1–1.5 × 10^2 cfu/ml for the antifungal assay. Testing was performed at 7.4 ± 0.2. Exactly 0.2 ml of the solution of test compound was added to 1.8 ml of seeded broth to form the first dilution. One ml of this was diluted with a further 1 ml of the seeded broth to give the second dilution and so on until six such dilutions were obtained. A set of assay tubes containing only seeded broth was kept as control and likewise solvent controls were also run simultaneously. The tubes were incubated in biochemical oxygen demand (BOD) incubators at 37 ± 1 °C for bacteria and 28 ± 1 °C for fungi. The minimum inhibitory concentrations (MICs) were recorded by visual observations after 24 h (for bacteria) and 72–96 h (for fungi) of incubation. Ciprofloxacin was used as a standard for the bacterial study while Amphotericin B was used as a standard for the fungal study.

3. RESULT & DISCUSSION

Physical data of the compounds **4a-4g** are given in the **Table 1**.

Table 1. Physical data of the compounds **4a-4g**

Compound	R	Yield (%)	Melting Point ◦C
4a	H	96	242- 243
4b	4-Cl	98	211 - 212
4c	2-Cl	92	235- 236
4d	4-CH_3	96	254- 255
4e	4-OCH_3	98	208- 209
4f	4-NO_2	94	284 - 285
4g	4-F	96	236 - 237

In vitro antibacterial and antifungal activity

Compounds **4a–4g** were tested for their antibacterial activity *in vitro* against *Staphylococcus aureus(SA) , Escherichai coli (EC), Klebsiella pneumonia(KP), Pseudomonas aeruginosa(PA)* and *Salmonella typhi (ST).* Ciprofloxacin was used as standard drug. Minimum inhibitory concentration (MIC) in µg/ml values shown in **Table 2**.

Table 2. In vitro antibacterial activity of compounds **4a–g**

Compound	Minimum Inhibitory Concentration (MIC) in µg/ml				
	SA	*EC*	*KP*	*PA*	*SA*
4a	100	200	200	200	100
4b	25	25	50	25	25
4c	25	25	50	25	25
4d	50	100	100	100	50
4e	50	100	100	50	50
4f	6.25	6.25	6.25	12.5	6.25
4g	3.13	3.13	6.25	3.13	3.13
Ciprofloxacin	25	25	12.5	25	25

All the 3,4-dihydropyrimidin-2(1H)-ones **4a–4g** exerted potent antibacterial activity *in vitro* against the tested bacterial strains. Moreover, compounds **4b**, **4c, 4f**and **4g** exerted excellent antibacterial activities aga inst *S. aureus, E. coli, K. pneumoniae, P. aeruginosa* and *S. typhi*. A comparative study of minimum inhibitory concentration for the compounds **4a–4g** using standard Ciprofloxacin *versus* bacterial strains given in **Fig. 2**.

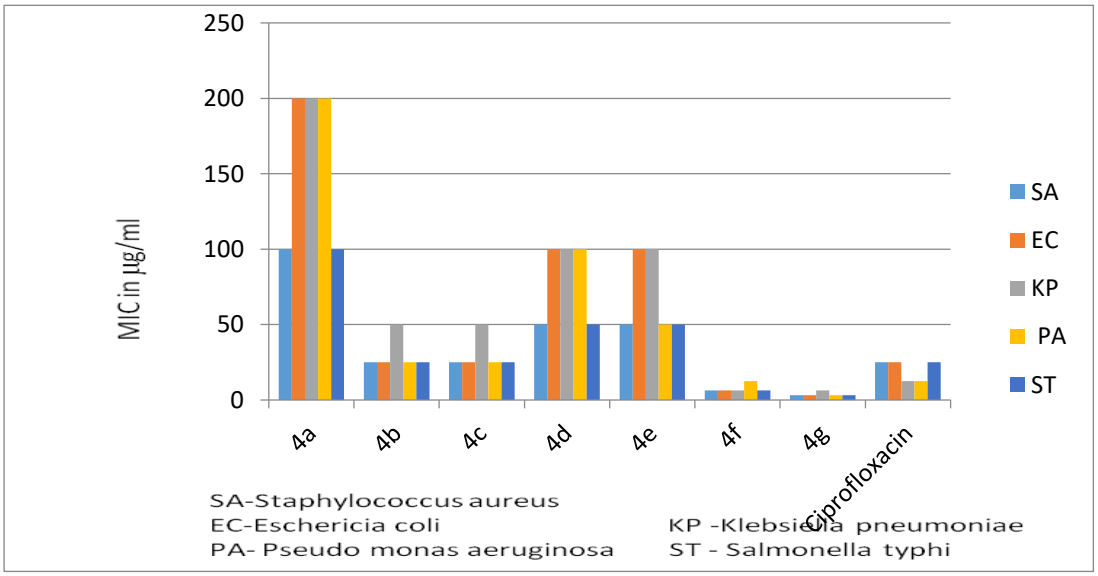


Fig. 2. Comparison of minimum inhibitory concentration of compounds **4a–g** with Ciprofloxacin (as standard) against bacterial strains from serial dilution method.

The *in vitro* antifungal activity of the synthesized compounds **4a–4g** was studied against the fungal strains viz., *Candida albicans (CA), Aspergillus flavus (AF), Rhizopus* and *Mucor*. Amphotericin B was used as a standard drug. Minimum inhibitory concentration (MIC) in µg/ml values is shown in **Table 3**.

Table 3. In vitro antifungal activity of compounds **4a–g**

Compound	Minimum Inhibitory Concentration (MIC) in µg/ml			
	CA	*AF*	*Rhizopus*	*Mucor*
4a	100	200	200	200
4b	25	50	25	25
4c	25	50	25	25
4d	50	100	50	50
4e	50	100	100	50
4f	6.25	6.25	12.5	6.25
4g	3.13	3.13	6.25	3.13
Amphotericin B	25	25	50	25

Compounds **4b**, **4c, 4f and 4g** exhibited excellent antifungal activities against all the tested fungal strains except *Mucor*. Minimum inhibitory concentration of compounds **4a–4g** were compared with standard Amphotericin B against fungal strains shown in **Fig 3.**

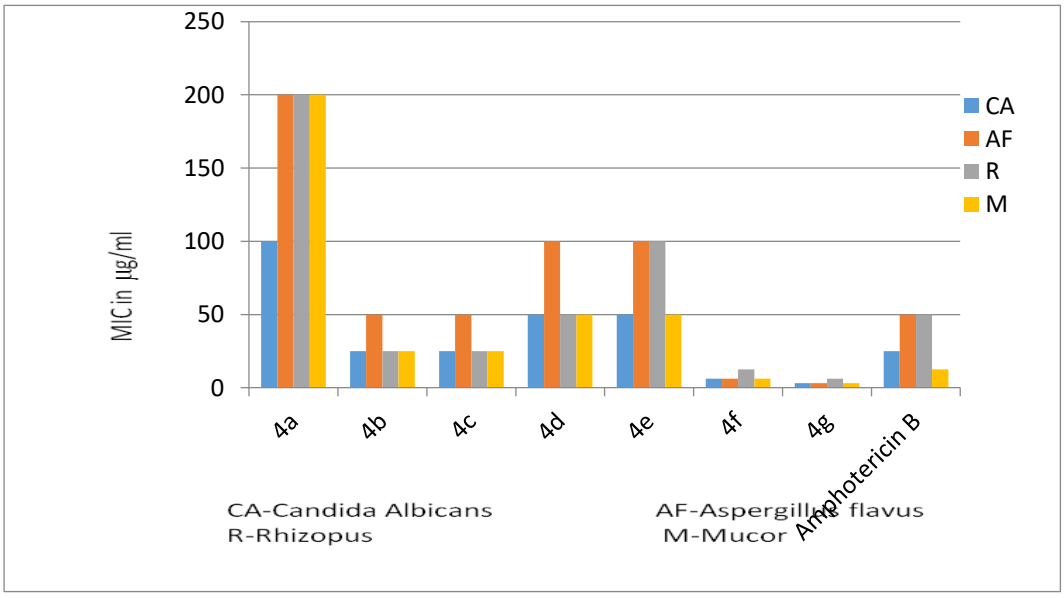


Fig. 3. Comparison of minimum inhibitory concentration of compounds **4a–g** with Amphotericin B (as standard) against fungal strains from serial dilution method.

4. Conclution

Results of this study show that compounds **4b**, **4c 4f** and **4g** which contain chloro, nitro and fluoro moieties exerted excellent antimicrobial activities against the tested organisms. Further development of this group of 3,4-dihydropyrimidinones may lead to compounds with better pharmacological profile than standard drugs and serve as templates for the construction of better drugs to come to blows bacterial and fungal infections.

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42

Synthesis and Spectral Characterization of Novel 1,2,4-Dithiazole Derivatives

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Abstract
A single step synthesis of N-(5-(substitutedimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (II a-d) was carried out by oxidative cyclisation of 2-(5-substituted-2,4-dithiobiureto) benzothiazole (I a-d) using liquid bromine in chloroform medium as an oxidizing agent. The products were isolated, characterized and justified on the basis of conventional chemical characteristics and spectral studies.
Key-words: Benzothiazole, oxidative cyclization, dithiazoles, oxidizing agent.

Introduction

Organic compounds containing thiadiazole as the heterocycles in their structure are identified for their biological activities, pharmaceutical activities, industrial applications, agricultural purposes and in medicinal sciences. Basically structure of thiadiazole is five membered nitrogen and sulphur containing heterocyclic compound. Presence of sulphur and nitrogen in its structure enhances the biological potential of the thiadiazole. Recently reported some newer thiadiazole along with pyridine for the anti-bacterial activities[1-2] and effect of germination pattern of jowar, Bhagwatkar[3] synthesized and reported the thiadiazole based triazine for the antibacterial activities and some different substituent's attached thiadiazole directly or indirectly shows effect directly in their biological, pharmaceutical and agricultural applications[4-5]. The benzothiazole based heterocycles are five membered heterocycles containing sulphur and nitrogen as a heteroatom were created its own background in the synthetic organic chemistry[6-10]. The biological as well as industrial applications of benzothiazole get enhanced, due the presence of the thiadiazole nucleus in their structure. Trusting the literature ideas in mind it is decided to design such organic moiety should contain thiadiazole along with the benzothiazole; to synthesize such series of benzothiazole based five member heterocycle containing sulphur and nitrogen as a heteroatom[11-17].
As a part of research work presently it has been planned to design and synthesize novel series of N-(5-(substitutedimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (II a-d) in this laboratory with the easiest and cheaper method by oxidative cyclisation of 2-(5-substituted-2,4-dithiobiureto) benzothiazole (I a-d) with liquid bromine in chloroform medium. The present method utilized somewhat suitable, convenient, cheaper, more practical utility and only a single step direct method for the synthesis of (IIa-d).

Experimental Section

Materials:

All chemicals used were of Mercks Millipore (Indian made). 2-(5-substituted-2,4-dithiobiureto) benzothiazole (I a-d) were prepared by known literature method[3] .

Method:

Method employed in the present experiments for the synthesis of series 1,2,4-dithiazole based benzothiazole is conventional refluxing under water bath for different hours for different experiments. The melting points of synthesized compounds were recorded using hot paraffin

bath and uncorrected. IR spectra were recorded on Perkin Elmer spectrometer in the range 4000-400 cm-1 in KBr pellets. PMR spectra were recorded on BRUKER AIIIANCE II 400 NMR spectrometer with TMS as an internal standard using CDCl3 and DMSO-d6 as a solvent. The purity of the compounds was checked on silica gel – G plates by TLC with layer thickness of 3mm.

General Procedure:

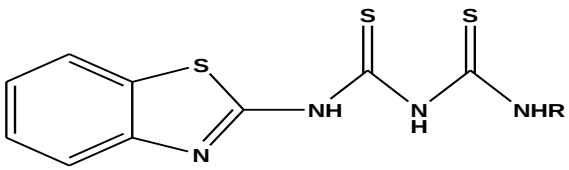
Experiment No. 1

Synthesis of N-(5-(allylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IIa):

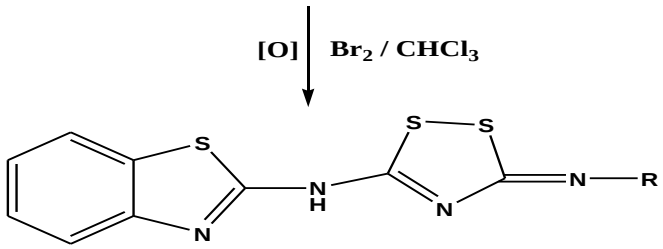
The pest of 2-(5-allyl-2,4-dithiobiureto) benzothiazole (Ia) was prepared in chloroform in a clean china dish and liquid bromine in chloroform was added with constant stirring at room temperature. During the addition of bromine in chloroform solution to the pest of (Ia), firstly the colour of bromine disappear, further addition of bromine in chloroform colour of bromine appears and persists. Such solution of bromine in chloroform and (Ia) kept for 4 hours at room temperature. Basification of the reaction mixture with dilute ammonium hydroxide solution gives the formation bright cream yellow coloured product (IIa). Recrystallization of the product was done using ethanol. Yield 89%, M. P. 172^0C.

Similarly, N-(5-(ethylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IIb), N-(5-(phenylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine(IIc), N-(5-(t-butylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IId) were synthesized from the oxidative cyclisation of 2-(5-ethyl-2,4-dithiobiureto) benzothiazole (Ib), 2-(5-phenyl-2,4-dithiobiureto) benzothiazole (Ic), 2-(5-t-butyl-2,4-dithiobiureto) benzothiazole (Id) with liquid bromine in chloroform medium respectively by the above mentioned method in Experiment No. 1 to 4 and the data obtained by the characterization of synthesized compound in a series (IIa-d) is given result section.

Reaction Scheme:



2-(5-substituted-2,4-dithiobiureto) benzothiazole (I a-d)



N-(5-(substitutedimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (II a-d)

Where R = -allyl, -ethyl, -phenyl, t-butyl

Results and Discussion:

Spectral data obtained from the present research support the formation of designed or target products. Spectral characterizations of all the synthesized compounds are also given below:

Data Analysis:

N-(5-(allylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IIa):
Cream Yellow solid, $C_{13}H_{11}N_3S_3$, Yield-89 %, M.P. 272, **FTIR (KBr) ν cm**-3085.89-3004.89 (Ar C-H stretching), 574.75(S-S stretching), 1587.31 (S-C=N stretching), 794.62-761.83 (C-S stretching); **^{1}H NMR (400 MHz CDCl3 δ ppm)**, doublet of 2H of –CH2 at δ 2.00 ppm, singlet of 1H of NH at δ 4.00ppm, pentate of 1H, doublet 2H and doublet of 2H of allyl at δ5.70ppm, 4.97ppm and 5.0ppm respectively and multiplet of 7H of Ph at δ 7.55-8.23ppm; Mol. Wt.:305.

N-(5-(ethylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IIb)
Dark Yellow solid, $C_{11}H_{10}N_4S_3$, Yield-92%, M.P. 168^{0}C, **FTIR (KBr) ν cm**-3085.89-3004.89(Ar-H Stretching), 574.75(S-S stretching), 1587.31(-C=N stretching), 794.62-761.83(C-S stretching),; **1H NMR (400 MHz CDCl3 δ ppm)**, triplet of 3H, -CH3 at δ0.90ppm, quartrate of 2H of –CH2 at δ 1.4ppm, multiplet of 7H, Ph at δ 6.52-8.01ppm, singlet of 1H, NH at δ 4.35ppm ; Mol. Wt.: 294.

N-(5-(phenylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine(IIc)
Yellow, $C_{15}H_{10}N_4S_3$, Yield-88%, M.P. 174ºC, **FTIR (KBr) ν cm**- 3056.96-3004.89 (Ar-H Stretching), 592.11 (S-S stretching), 1587.31 (-C=N stretching), 794.62-761.83 (C-S stretching),; **1H NMR (400 MHz CDCl3 δ ppm)**, multiplet of 12H, Ph at δ 6.11-8.02ppm and singlet of 1H, -NH at δ4.34ppm; ESI-MS (m/z) gives base at m/z+=226.98, 74.90, 359.93 and molecular ion i.e. molecular weight is 342.

In the present work is best cheaper and less time consuming method of cyclisation of organic compound. Route of mechanism of the present synthesis is due to the conjugation of amido-H with thionyl Sulphur. Among all the synthesised of compounds (IIa-IId), percentage of yield of compound (IIb) is highest i.e. 92%.. However (IIa) and (IId) shows comparable yield with the (IIb).

Conclusion

In all the synthesized compounds, maximum yield of (IIb) displays ethyl group is electrometrically donating group on nitrogen in 2,4-dithiobiurets with increases the rate of reaction by giving its electrons.

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43

Synthesis of Substituted Flavanones and their Impact on Seed Germinations

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ABSTRACT:

As a part of systematic investigation, spectral analysis and morphology (root and shoot elongation) of a several chlorosubstituted flavanones from diketones, gives various series by using different aldehydes. As in series, 3-methoxy-8-chlorobenzoylflavanone,3-chlorobenzoyl-8-chloroflavanone,3-benzoyl-8-chloroflavanone.

KEWORDS;- Diketones, flavanones, root and shoot elongation.

INTRODUCTION:

Flavanones are group of common natural polyphenolic compound that are widely found in plant kingdom. It consists of two aromatic ring links through three Carbon bridge with a carbonyl function. Actually these are the class of Flavanoids, which can be subdivided into several classes such as chalcone, flavanones, isoflavanones, aurones etc. The flavanones are mainly distributed in citrus fruitsIn present study, various chlorosubstituted flavanones were synthesized from chlorosubstituted diketones and screened for their morphology (i.e. root and shoot elongation) against some crop plants. Flavanones and their analogues having attracted considerable attention because they possess antioxidant effect, cytotoxic, antimicrobial. Antinflamatory activities etc.

Larget R et.al.[1] reported substituted flavanone & studied as neuroprotective agents. Venkatramn et.al[2] synthesized the flavanone from chalcone by dehydrogenation with SeO2. Yoigtandes et.al. [3] reported the flavanone from flavanone by heating with I_2. Patill[4] synthesized flavanone from by using F2/DMSO as a dehydrogenating agent. Mayer A.M.et.al[5] synthesized cumarine and their role as growth regulators in several plants.. Korade D.L. et.al.[6] reported the effect of Anthracenes on seed germination of *Lolium multiflorum* plants. Gibba Z. et.al.[7] studied the effect of nitric oxide on germination of *Empress tree* seeds.Majumdar, G. p.[8] reported studied the cambial activities of root habit and shoot development in some plants.

The reaction of diketones with various aldehydes gives various flavanones these reactions carried out in presence of ethanol as energy transfer medium in aq.KOH.

It has been well established that, the presence of chlorosubstituted ketones present in flavanones, with the hope that the resulting molecules would exhibit promising root and shoot elongation as shown in table and graph.

EXPERIMENTAL METHODS:

All the glassware's used in the present work were of Pyrex quality. Melting points were determined in open capillary and are uncorrected. Purity of compounds was monitored on silica gel coated TLC plate. I.R. spectra were recorded on SHIMADZU Spectrophotometer in KBr

palates. The analytical data of compounds were highly satisfactory. All the chemicals used were of analytical grade. All the solvents used were purified by standard methods. Physical characterization data of all the compounds are given in Table 1.

Result and discussion

The synthetic methods used in present work are given below along with their, IR data.

Acetylation of P- Chlorophenol:

P – Chlorophenol 50 ml was mixed with acitic unhydride 60 ml & unhydrus sodium acetate 5 gm the mixture was refluxed for bout on 1 hrs. it was cooled and poured into cold water. Acetated layer was separated & washed with water several times finally it was purified by distillation and the distillate of compound was collected at about 232^0C. Yield 75%, B.P. 232^0C

2 – Hydroxy 5 – chloro-acetophenone:

When Phenyl acetate (50ml) was mixed with anhydrous $AlCl_3$ (120gm) & heated at 120^0C for 45 min on oil bath. The reaction mixture was decomposed with ice cold water containing little hydrochloric acid to get crude ketone. It is purified by dissolving in acetic acid & allowing the solution to fall drop by drop into cold water with stirring. A slightly yellow powder was obtained having M.P. = 86^0C, Yield = 72%

2 – Benzoyloxy 5 - chloroacetophenone:

2 – Hydroxy 5- Chloroacetophenone (0.04 mol) & (8.59 ml) Benzoyl Chloride (0.05 mol) were dissolved in NaOH (10 %) (30 ml). The reaction mixture was shaken for about 45 min. The product thus separated filtered, washed with water followed by sodium bicarbonate (10%) again with water. The solid product was crystallized from ethanol to obtain. 2 – benzoyloxy 5-chloroacetophenone white crystal is obtained having M.P. - 87^0C, Yield - 80%.

1 – (2-hydroxyl Phenyl) 5 – Chloro- 3 – Phenyl – 1, 3 – Propanedione:

2 – Benzoyloxy 5 - chloroacetophenone (1.5 gm) was dissolved in (40 ml) dry Pyridine. The solution was warmed up to 60^0C pulverized KOH (15gm) was added slowly with constant stirring. After 4 hours of heating then reaction mixture was acidified by adding ice cold HCl (1 : 1). The brownish yellow solid product thus separated was filtered, washed with sodium bicarbonate solution (10%) and finally again with water. It was then crystallized from ethanol-acetic acid mixture to get 1 – (2-hydroxyl phenyl) 5 – Chloro -3 – Phenyl – 1, 3 – Propanedione. M.P:121^0C, Yield – 75 %.

3 – benzoyl - 8 – chloro flavanone:

A mixture of 1 – (2-hydroxyl phenyl- 5 – Chloro 3 – Phenyl – 1, 3 – Propanedione (0.01 mol) (3 gm) & Benzaldehyde (0.12 mol) (1 ml) was refluxed in ethanol (25 ml) and KOH (1 gm) for 15 – 20 min descried to get compound M.P. - 230^0C, Yield - 79%.

3 – Methory – 8-chloro benzoyl flavanone:

A mixture of 1 – (2-hydroxyl phenyl)-3 – phenyl – 1, 3 – propanedione (0.01 mol) (3 gm) & anisaldehyde (0.12 mol.) (1 ml) was refluxed in ethanol (25 ml) & KOH (1 gm) for 15 -20 min. & process as descried to get compound, 3 – methoxy-8 – chloro benzoyl flavanone. M.P. - 251^0C, Yield – 72 %.

Table (1): Characterization data of synthesized new compound

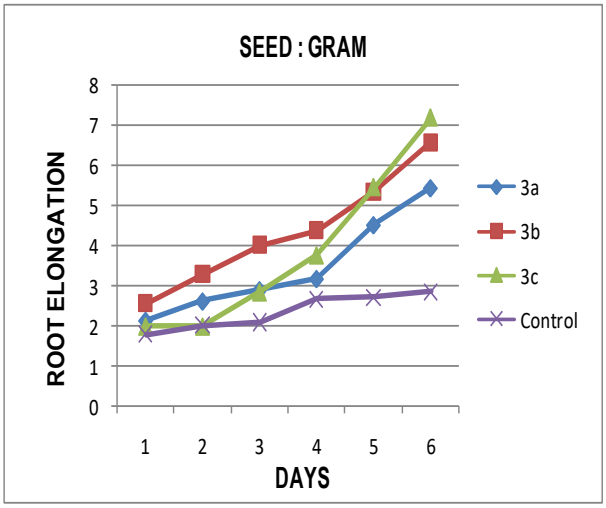
Compound	Molecular Formula	M.P. (°C)	Yield (%)	Rf
3a	$C_{21}H_{13}O_3Cl$	230	79	0.76
3b	$C_{22}H_{16}O_4Cl$	251	75	0.78
3c	$C_{21}H_{14}O_3Cl_2$	240	75	0.79

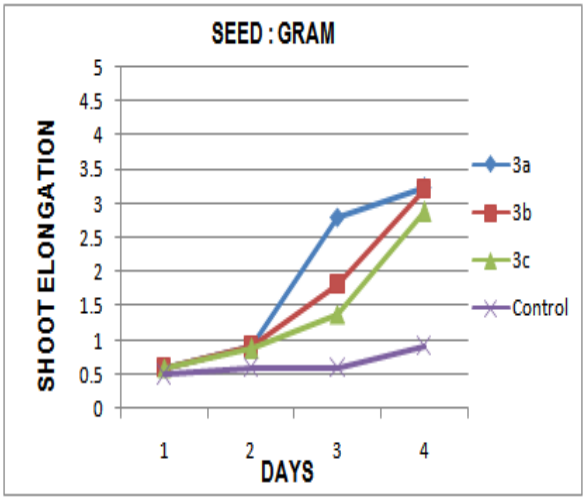
TABLE NO. 1 : SEEDS - *GRAM*

Sr. No.	Comp.	% of germination Day					Average length of root in cm. Day						Average length of shoot in cm. Day					
		2	4	6	8	10	2	4	6	8	10	12	2	4	6	8	10	12
1	3a	80%	100%				1	2	2.4	3.2	3.5	4			0.6	0.9	2.8	3.2
2	3b	80%	100%				1	1.5	2	2.7	3.2	3.9			0.6	0.9	1.8	3.2
3	3c	100%	100%				2	2.4	2.6	3.4	3.7	4			0.6	0.9	1.4	2.9
4	Control	80%	90%				0.5	1.2	1.4	2	2.5	2.7			0.5	0.6	0.6	0.9

TABLE NO. 2 : SEEDS - *Black Eyed Beans (Chawali)*

Sr. No.	Comp.	% of germination Day					Average length of root in cm. Day						Average length of shoot in cm. Day					
		2	4	6	8	10	2	4	6	8	10	12	2	4	6	8	10	12
1	3a	80%	100%				2.1	2.6	2.9	3.2	4.5	5.4			0.6	0.9	2.8	3.2
2	3b	80%	100%				2.6	3.3	4.0	4.4	5.4	6.6			0.6	0.9	1.8	3.2
3	3c	80%	100%				2.6	3.3	4.0	4.4	5.4	6.6			0.6	0.9	1.8	3.2
4	Control	80%	90%				1.8	2	2.1	2.7	2.7	2.9			0.5	0.6	0.6	0.9





Conclusion

The present study was aimed at investigating the impact of newly synthesized substituted flavanone on some crop plants viz: *Gram* and , *Black Eyed Been (Chawali)*. The choice of these crops was based on their enormously vast utility and also the indispensability for the survival of the human race, all across the globe.

The efforts have been made to investigate and analyze the convergence and divergence effect of test compounds on the morphology of plants under investigation. It was interesting to note that, all the treated seeds exhibited remarkable roots and shoots elongation as compared to untreated ones.

When the growth of all the treated plants were compared among themselves, it was distinctly observed that, the change which is dominant while applying the treated compound i.e. chlorosubstituted flavanones in *Gram, Black Eyed Been (Chawali).* In the initial stage vegetative growth was not significance but after 2nd interval it gradually increases and after 12 days roots and shoots elongation were dominant to a considerable extent. Thus there has been fair amount of satisfaction in crying out the present study. The encouraging results have surely contributed to the enthusiasm of the author. But honestly, this is just the beginning. There is a much scope for further study, and there is a long way to go.

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44

Antimicrobial Resistance : A Global Challenge

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ABSTRACT

Decades after the first patients were treated with antibiotics, bacterial infections have again become a threat because of the rapid emergence of resistant bacteria .Multidrug resistant urinary tract infection is a most problematic infection and it is very difficult to doctors to manage the patient by using appropriate antibiotics due to development of multidrug resistant strains of bacteria . MDR strains shows resistant to maximum number of antibiotics and sensitive to very few antibiotics.

Keywords : Urinary tract infection , multidrug resistant , antibiotic , bacteria

INTRODUCTION:

The bacterial associated Urinary Tract infection is most common infection found in all ages and both the genders offering antibiotic resistance in most of the cases of infection. Now a day's antibiotic resistance has becomes major public health problem leads to increase resistant to huge number of antibiotics from few years. The antibiotics are also responsible to develop multidrug resistant strain due to resistance genes of resistant bacteria .The rapid emergence of antibiotic resistant transfer genes among uro-pathogens are important cause of development of antibiotic resistance. The increased antibiotic resistant suggest that the choice of antibiotic should be guided by culture and sensitivity assay. In past decades many kind of resistant strains are discovered.

PRINCIPLE OF ANTIMICROBIAL THERAPY

The objective of antibacterial therapy is to eliminate the bacterial growth in the urinary tract and the antibiotics used are efficacious, safe, and cost effective. The basic c treatment starts with the antibiotics which are number of choices available in market. The resolution of infection is dependent on the susceptibility of the bacteria to the concentration of the antibiotic achieved in urine. Antibiotics should eliminates the bacterial growth in urinary tract when proper antibiotics are used which is able to achieve level in urine and the duration that this level remains above the minimum inhibitory concentration (MIC) of microorganism that attack on urinary tract. (Hooton TM, 1991). An effective antibacterial usually achieved MIC both in serum and urine of healthy adults, the urinary level often many folds greater than serum level. However the serum levels are critical in patients with uro-sepsis and urinary tract infection involving renal parenchyma. (Jacobson SH, 1991)

Resistance to B-Lactams

Urinary bacteria may develop several mechanisms of resistance to Blactams which is most efficient method of resistance to these agents in Gramnegatives is the synthesis of B-lactamases. B- lactamases have presumably evolved to fight natural B-lactams, produced by bacteria such as Streptomyces, Lysobacter , penicillium or Acremonium. (Brakhage AA,

2005). However the widespread administration of antibiotics is influenced the development of B- lactamases mediated resistance. Since B- lactam antibiotics came into clinical use, B-lactamases are evolved with them. The emergence of MBL mediated resistant among enterobacteriacae has also becomes serious health concern. More ever the increase in international travel is likely to be contributory factor for the ascendancy of mobile MBL genes as much as the mobility among individual bacteria.

Resistance to Colistin

Colistin belongs to the antimicrobial class of polymyxin and acts by binding to the lipid a moiety of the bacterial lipopolysaccharide and subsequently disintegrating the bacteria membrane. Resistance to colistin associated with lipopolysacharide modification leading to a high level of antibiotic non-susceptibility

Resistance to Tigecycline

Tigecycline is first glycylcycline to be approved by the FDA, may lose its activity against MDR strains, particularly when low drug concentration are attained in the serum during treatment. Resistance develops when the MIC of the targeted pathogen exceed the Cmax of the drug, which is almost the rule for all targeted A. baumannii strains. According to molecular studies efflux pumps seem to be the most important mechanism of resistance to tigecycline both in enterobacteriacae and non-fermenting rods.

Resistance to Fluoroquinolone

Fluoroquinolone such as ciprofloxacin with bactericidal activity against gram negative pathogens. Fluoroquinolone act by binding to the nuclear enzyme DNA gyrase and topoisomerase IV. In spite of particular targets, resistance mechanisms both chromosomal and plasmidic have been developed. Chromosomal resistance mechanism includes target mutation and augmented expression of efflux pumps.

CONCLUSION:

Antibiotic therapy is a choice of treatment for the bacterial infections , but due to development of multidrug resistant strains the antibiotics are not effective as a treatment to patient. New antibiotic developed which may be the used as a antibiotic therapy in future in resistant cases. The present review is helpful to know few multidrug resistant pathogens are sensitive to particular antibiotics and the proper antibiotic has been administrated to patient for rapid cure of infection.

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45

Wings across Reservoirs: Understanding and Safeguarding the Migration Patterns of Insectivorous Birds in Anthropogenic Landscapes

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ABSTRACT:

The migration patterns of insectivorous birds in reservoir dams play a vital role in ecosystem dynamics, influencing insect populations and contributing to overall biodiversity. This research investigates the intricacies of bird migration in the specific context of reservoir dams, focusing on insectivorous species and their seasonal movements. The study aims to understand the routes, patterns, and ecological implications of bird migration in these anthropogenic environments. The research delves into the ecological role of insectivorous birds in reservoir dams. Preliminary analyses suggest a substantial impact on insect populations, with potential cascading effects on the broader ecosystem. Understanding these ecological dynamics is crucial for effective reservoir dam management and conservation. The study's findings have implications for reservoir dam management, emphasizing the need for conservation strategies that consider the ecological importance of these birds in maintaining ecosystem balance.

Keywords: Bird migration, insectivorous birds, reservoir dams, ecosystem dynamics.

INTRODUCTION:

Bird migration, a phenomenon deeply ingrained in the evolutionary tapestry of avian species, plays a pivotal role in ecological systems worldwide. The intricate journeys undertaken by birds across vast distances are essential for maintaining biodiversity, influencing insect populations, and contributing to ecosystem resilience. In this context, our research focuses specifically on the migration patterns of insectivorous birds within the unique environment of reservoir dams.

1.1 Background: Reservoir dams, man-made structures designed primarily for water storage, have become integral components of the human landscape. These environments, often shaped by anthropogenic influences, present a distinctive ecosystem where wildlife, particularly avian species, adapts to novel challenges. Insectivorous birds, a diverse group with varied migratory behaviors, find themselves navigating these artificial landscapes.

1.2 Importance of Studying Bird Migration in Reservoir Dams: Understanding bird migration in reservoir dams is not merely an academic pursuit but a necessity for effective environmental management. Reservoir dams, with their altered landscapes and proximity to human activities, pose unique challenges to avian species. Insectivorous birds, reliant on specific habitats and food sources, become crucial indicators of the ecological health of these environments.

As reservoir dams serve multifaceted roles, from water supply to energy production, their impact on local ecosystems extends beyond their primary function. Our study recognizes the need to explore how these human-altered landscapes influence the migratory behaviors of insectivorous birds, species that contribute significantly to pest control and ecosystem balance.

1.3 Specific Focus on Insectivorous Birds: The choice to concentrate on insectivorous birds stems from their ecological significance. These avian species, characterized by their diet primarily consisting of insects, fulfill essential roles in regulating insect populations. As they traverse vast distances during migration, their interactions with the environment become intricate ecological narratives. By studying the migration patterns of insectivorous birds, we aim to unravel the complexities of their journeys and comprehend their contribution to the ecological equilibrium of reservoir dam ecosystems.

1.4 Research Question and Objectives: At the heart of this study lies the fundamental question: How do insectivorous birds navigate and contribute to ecosystem dynamics in the context of reservoir dams? To address this question, our research objectives are as follows:

- To identify the insectivorous bird species inhabiting reservoir dam environments.
- To analyze the migration routes and patterns of these bird species.
- To investigate the influence of environmental factors, such as climate and food availability, on the migration behaviors of these birds.
- To assess the ecological consequences of alterations in migration patterns within reservoir dams.

This research seeks not only to enhance our understanding of bird migration in anthropogenic landscapes but also to provide valuable insights for conservation strategies tailored to the unique challenges presented by reservoir dam environments.

LITERATURE REVIEW:

2.1 Bird Migration Studies: Bird migration, a phenomenon studied for centuries, has been a subject of fascination and scientific inquiry. Classical migration studies often focused on well-known flyways, such as the East Atlantic Flyway or the East Asian-Australasian Flyway, tracking the movements of waterfowl and shorebirds. While these studies have significantly contributed to our understanding of long-distance migration, the dynamics of migration within human-altered landscapes, such as reservoir dams, remain relatively understudied.

2.2 Migration in Anthropogenic Environments: The impact of human activities on bird migration patterns has gained attention in recent decades. Urbanization, deforestation, and climate change have altered the traditional routes and behaviors of migratory birds. However, the specific influence of reservoir dams, with their unique combination of altered habitats and human activities, merits closer examination. Some studies have explored how artificial water bodies affect bird migration, but the focus on insectivorous species within reservoir dams remains limited.

2.3 Significance of Insectivorous Birds in Ecosystems: Insectivorous birds, a diverse group encompassing species from various families, play crucial roles in maintaining ecological balance. Their diet primarily consists of insects, making them natural regulators of pest populations. In agricultural landscapes, insectivorous birds contribute to integrated pest management, reducing the need for chemical interventions. However, the extent of their contribution in reservoir dam ecosystems and the potential consequences of altered migration patterns remain underexplored.

2.4 Environmental Factors Influencing Bird Migration: Numerous environmental factors influence bird migration, including climate conditions, food availability, and habitat changes. Climate change, in particular, has been identified as a significant driver of alterations in migration patterns. Understanding how these factors intersect within the context of reservoir

dams is crucial for predicting and mitigating potential ecological disruptions. The literature review seeks to identify key studies that have examined the interplay between environmental factors and bird migration in both natural and artificial environments.

2.5 Gaps in Current Knowledge: Despite the wealth of information available on bird migration, there is a noticeable gap in literature concerning insectivorous birds in reservoir dams. Existing studies often focus on waterfowl or larger species, neglecting the ecological nuances associated with insectivorous behaviors. This literature review underscores the need for targeted research that specifically addresses the migration patterns, behaviors, and ecological roles of insectivorous bird species within reservoir dam environments.

METHODOLOGY:

3.1 Study Sites Selection: The choice of study sites is a critical aspect of our methodology. Reservoir dams selected for this research are characterized by diverse ecological settings, representing different climatic zones and geographic regions. This diversity ensures a broad understanding of how insectivorous birds adapt to various environmental conditions within reservoir dams.

3.2 Field Observations and Behavioral Analysis: Continuous field observations will complement the technological aspects of our methodology. Researchers will spend extended periods at the selected study sites, documenting bird behaviors, feeding patterns, and interactions with the reservoir dam environment. Behavioral analysis will focus on understanding how insectivorous birds adapt to the altered habitats presented by reservoir dams, including changes in foraging behavior and nesting preferences.

3.3 Climate and Habitat Analysis: Environmental factors, such as climate conditions and habitat changes, are integral components of our study. Climatic data will be collected to correlate with bird migration patterns, exploring the influence of temperature, precipitation, and seasonal variations on migration behaviors. Habitat analysis involves assessing the availability of insect prey, vegetation cover, and water quality within reservoir dams.

3.4 Data Analysis: The collected data will undergo rigorous analysis. Statistical methods will be applied to identify migration hotspots, determine seasonal variations in bird populations, and assess correlations between environmental factors and migration behaviours. Geospatial tools will aid in mapping migration routes and stopover locations.

3.5 Ethical Considerations: All aspects of the research adhere to ethical standards and prioritize the well-being of the studied birds. Bird handling follows established protocols to minimize stress and potential harm. The research team has obtained necessary permits and approvals from relevant wildlife conservation authorities, ensuring compliance with legal and ethical guidelines.

3.6 Community Engagement: Recognizing the importance of community involvement, our methodology includes outreach programs to engage local communities residing near the selected reservoir dams. Workshops, awareness campaigns, and citizen science initiatives aim to foster a sense of shared responsibility for the conservation of insectivorous birds and their habitats.

3.7 Limitations: While our methodology is comprehensive, certain limitations are inherent in avian migration studies. External factors such as predation, disease, and unforeseen events may impact the reliability of data collected through bird banding and satellite tracking. However, the combination of multiple data sources enhances the robustness of our findings.

CASE STUDIES:

4.1 Case Study 1: The Warbler's Journey *Species:* Black-and-white Warbler (*Mniotilta varia*) *Migration Route:* Northeastern study site to Central America *Key Findings:* This case study reveals a remarkable migratory journey of Black-and-white Warblers navigating from a northeastern reservoir dam to their wintering grounds in Central America. Satellite tracking data indicated distinct stopover points in areas with abundant insect populations, emphasizing the critical role of reservoir dam habitats in supporting migratory journeys.

4.2 Case Study 2: Navigating Urban Reservoirs *Species:* Common House Martin (*Delichon urbicum*) *Migration Route:* Urban reservoir dams in European settings *Key Findings:* In contrast to traditional rural habitats, this case study explores the migratory patterns of Common House Martins within urban reservoir dams. These insectivorous birds demonstrated adaptive behaviors, utilizing artificial structures for nesting and displaying adjusted migration routes influenced by urban landscape features.

CONSERVATION STRATEGIES:

5.1 Habitat Restoration and Enhancement: Implementing habitat restoration initiatives within reservoir dams involves reestablishing native vegetation, maintaining suitable nesting sites, and creating insect-rich environments. This strategy aims to ensure that migratory birds find optimal conditions for feeding, resting, and breeding.

5.2 Climate-Responsive Conservation: Given the influence of climate on bird migration, conservation efforts must be adaptive to changing climatic conditions. Integrating climate-responsive strategies involves monitoring climate trends, understanding their impact on bird behavior, and adjusting management practices accordingly.

5.3 Community-Based Conservation: Engaging local communities in the conservation process is paramount. By fostering awareness, providing education, and involving communities in citizen science initiatives, a sense of shared responsibility is cultivated. Local support contributes to sustainable conservation practices and the protection of reservoir dam ecosystems.

5.4 Sustainable Development Practices: Promoting sustainable development around reservoir dams ensures the coexistence of human activities and wildlife conservation. Implementing regulations that minimize disturbances, control pollution, and prioritize ecosystem health contributes to the long-term viability of insectivorous bird populations.

CONCLUSION:

This research has delved into the intricate world of insectivorous bird migration within reservoir dams, uncovering diverse patterns, adaptive behaviors, and ecological interactions. The case studies underscore the importance of these avian species in maintaining ecological balance and pest control within human-altered landscapes.

The conservation strategies proposed emphasize a holistic approach that integrates habitat restoration, climate-responsive measures, community engagement, and sustainable development practices. Preserving the migratory routes of insectivorous birds is not only vital for their well-being but also contributes to the overall health and resilience of reservoir dam ecosystems.

As we navigate an era marked by rapid environmental changes, understanding and safeguarding the migratory journeys of insectivorous birds become imperative. This research serves as a stepping stone towards comprehensive avian conservation strategies, bridging the

gap between scientific knowledge and on-the-ground initiatives. The journey of these birds, intertwined with the ecosystems of reservoir dams, unveils a narrative of adaptation, resilience, and the delicate balance between human activities and the natural world.

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46

Synthesis and Characterization of Pyrazolone and its derivatives.

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Abstract:

The synthesis of pyrazolone and its derivatives is achieved by a clean, one-pot, multi-component condensation reaction combining ethyl acetoacetate, hydrazine hydrate, aromatic aldehyde in catalytic amount of MSA. This approach has numerous benefits, including a quick reaction time and an easy work-up process. Compounds were identified via mass spectral analysis, NMR, IR, and chemical transformation.

Keywords: aryl aldehyde, ethyl acetoacetate, hydrazine hydrate, MSA, pyrazolone etc.

Introduction

Pyrazolone are a class of organic compounds that feature a five-membered ring containing three carbon atoms and two nitrogen atoms. The molecular formula of pyrazolone is $C_3H_3N_2$. This heterocyclic ring structure imparts unique chemical and pharmacological properties to pyrazolone, making them significant in various fields such as chemistry and medicine. Pyrazolone also exhibit interesting coordination chemistry, forming complexes with various metal ions. This property makes them relevant in coordination chemistry and catalysis.The chemical, pharmaceutical, and agrochemical industries are very interested in pyrazolone derivatives[1,2]. Considered an active scaffold with pharmacological importance, pyrazolone and its derivatives exhibit nearly all pharmacological activity. The pyrazolone moiety's pharmacological potential has been demonstrated by the nucleus's presence in pharmacological agents belonging to various therapeutic categories, including rimonabant, difenamizole, an analgesic; fezolamide, an antidepressant; and celecoxib, a potent anti-inflammatory and antipsychotic.[3] Because of their many characteristics and uses, pyrazolones are a class of chemicals that have been studied. These include pyrazol-3-ol and pyrazolin-5-one. Sulfamazone, propyphenazone, and nifenazone[4] are a few of the exploratory small compounds containing pyrazolone that have been considered as potential therapeutic possibilities. Derivatives of pyrazolone are a significant class of heterocyclic chemicals found in numerous medications and synthetic goods. Based on a review of the literature, pyrazolone derivatives exhibit a range of pharmacological actions, including, anti-tubercular[5], anti-fungal,[6,7] anti-bacterial,[8] anti-inflammatory,[9] anti-timor,[10] anti-microbial.[11]

In this study, we have created a sophisticated, effective, simple, and straightforward method for the synthesis of pyrazolone and its derivatives. We do this by employing ethanol as a solvent together with hydrazine hydrate, ethyl acetoacetate, and substituted aryl aldehydes in a catalytic quantity of MSA. In terms of environmentally friendly procedures, the combination of the green technique and the catalyst results in an outstanding product yield. This approach offers many important benefits, including reduced reaction time, solvent-free conditions, atom economy, using a green catalyst, and a more pleasant workup process.

Experimental

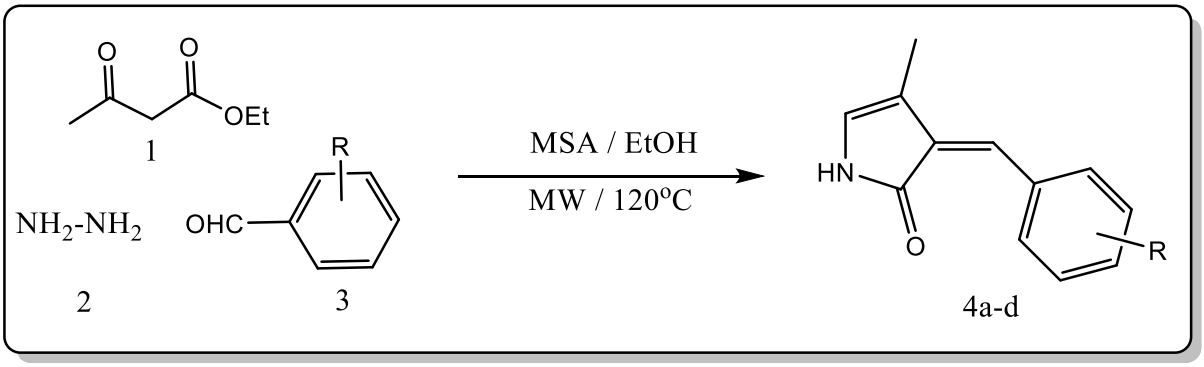
General

The digital melting point device (Veego-VMD) was used to record the uncorrected melting point of the produced chemical. A.R. Grade chemicals were used. Every chemical employed was of A.R. Grade, and it wasn't purified further. Microwave irradiation was carried out in a Microwave Oven, Model No. MS2079 DB DB1QILN (2450 MHz, 1050 W) equipped with

Erlenmeyer flask. The compound's melting point was measured in an open capillary tube and might not be accurate. Using an FT-IR spectrophotometer made by Perkin-Elimer, IR spectra were recorded. KBR Pellet. Using chloroform as a solvent, the 1H NMR spectra and mass were recorded using a Perkin-Elimer spectrophotometer. The chemical shift value was reported in parts per million (ppm) with respect to TMS, which served as an internal standard.

General Procedure for the synthesis of Pyrazolone and its Derivatives

The combination of **1**ethyl acetoacetate (0.01mmol), **2**hydrazine hydrate (0.01mmol), and **3** aryl aldehyde (0.01mmol) in catalytic amount of Methane sulphonic acid (MSA) in an Erlenmeyer flask and irradiated until completion of the reaction in microwave oven.The reaction mixture was poured in crushed ice and filtered, washed with ethyl acetate, the product was recognized as 3-methyl-4-arylidene pyrazolone (4a-d). The crude product was collected and recrystallized in ethanol and dried. The entire product was characterized by physical constant and spectroscopic techniques and compared with the standard method.



Scheme 1

Result and Discussion

As indicated in the scheme 1, we reported a direct method for the synthesis of pyrazolone and its derivatives by one pot condensation of aromatic aldehyde, hydrazine hydrate, and ethyl-acetoacetate.The yield was really high. In order to assess the extent and constraints of the methodology, the reactions were conducted in the absence of a catalyst, and the structures of all newly synthesized pyrazolone derivatives were established using chemical transformation, NMR, IR, and mass analysis.

Table1: Synthesis of pyrazolone & its derivatives catalyzed by MSA under M.W. (120oC/300W)

Product	Name of compound	% yield	Melting Point in ^{O}C
4a	(Z)-3-benzylidene-4-methyl-1,3-dihydro-2H-pyrrol-2-one	94%	122 ^{0}C
4b	(Z)-3-(4-chlorobenzylidene)-4-methyl-1,3-dihydro-2H-pyrrol-2-one	89%	215 ^{0}C
4c	(Z)-4-methyl-3-(3-nitrobenzylidene)-1,3-dihydro-2H-pyrrol-2-one	87%	195 ^{0}C
4d	(Z)-3-(4-hydroxybenzylidene)-4-methyl-1,3-dihydro-2H-pyrrol-2-one	92 %	197 ^{0}C

Table 2. Optimization of catalyst concentration of (4b) under M.W. Irradiation

Entry	Catalyst mol %	Time, min	Yields %
1	No catalyst	9	-
2	1	8	76
3	2	7	89
4	**3**	**3**	**95**
5	4	5	85
6	5	8	70

Initially, the mixture of Ethyl acetoacetate, Hydrazine hydrate and substituted aryl aldehydes, (0.01 mol each) was taken in an 50 mL vessel and subjected to microwave irradiation under neat conditions in the absence of catalyst and solvent, and the reaction was failed to get the product under this condition. The reaction was repeated in the presence of catalyst in the range 1-5 mol %. We have optimized the amount of catalyst for the synthesis of (**4b**, Table 1) under microwave irradiation and excellent yield was obtained in only 3 minutes when 3 mol % catalysts are introduced (**Table 2,** entry 4).

Spectroscopic characterization.

4c) (Z)-4-methyl-3-(3-nitrobenzylidene)-1,3-dihydro-2H-pyrrol-2-one

Solid: - Melting point = 195ºC

IR (KBr, Cm^{-}1) : 1354, 1260, 1500, 1607, 670.

^{1}HNMR (400 MHz, DMSO-d6):δ 7.2(1H,s), 1.18 (1 H, s), 6.93 (1 H, s), 8.10-8.12 (4H, m).

4d) (Z)-3-(4-hydroxybenzylidene)-4-methyl-1,3-dihydro-2H-pyrrol-2-one

Solid: - Melting point = 197ºC

IR (KBr, Cm^{-}1) : 1354, 1260, 1500, 1607, 670.

^{1}HNMR (400 MHz, DMSO-d6): δ 7.45(1H,s), 6.89 (1 H, s), 9.81 (1 H, s), 5.0(1H,s), 6.93 (4H, m).

Conclusion

We have been able to offer an effective method for the synthesis of pyrazolone derivatives in the presence of MSA in our current study. All of the recently synthesized compounds' structures were determined via mass spectral analysis, NMR, IR, and chemical transformations.

Condensation-enhanced pyrazolone synthesis and its derivatives provide high yields of pyrazolone in good quality and purity at a low cost.. This approach has the noteworthy advantages of being catalyst-free and having an easy workup procedure. The synthesis process used to create these molecules is very easy to use, clean, economical, green, and environmentally friendly**.**

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47

Preliminary Phytochemical analysis of Leaves extract of the plant *Justicia Adhatoda*

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Abstract:

The well-known Indian medicinal herb Justicia adhatoda is knowned for its pharmacopoeia. This plant has been used commonly in the ayurvedic system of medicine. This plant's root, bark, leave and flower are used to heal many types of infection. In the present study, we have done the phytochemical screening of its leaves for glycoside, flavonoids, tannin, alkaloid, phenols, terpenoids and steroids and in the prepared hydroalcoholic extracts using Soxhlet extraction method

Key Words: Phytochemical Analysis, *Justica Adhatoda* plant.

Introduction:-

Justicia adhatoda is a member of family Acanthaceae which is a small evergreen herbal plant. This plant is distributed all over the India. All the parts of this plant has been used for their curative effects from ancient times[1]. *J. adhatoda is* a widely used plant medication in Unani and Ayurvedic medicin[2]. Justicia adhatoda produces vasicine, which is used to treat a variety of illnesses, primarily respiratory tract conditions. In Sweden *J. adhatoda* is classified as a natural remedy and some preparations based on protocols against cough containing an extract of J. adhatoda are accessible[3].

It is used by Ayurvedic physicians and possesses some medicinal properties. It has been used to treat a wide range of illnesses, most notably those affecting the respiratory system. As a result, it is one of the main herbs in the Ayurvedic system and is used to treat asthma, bronchitis, cough, and cold symptoms[4]. It has been used to control both internal and external bleeding such as peptic ulcers, hemorrhoids, bleeding gums and also used for a multitude of disorders including; leprosy, blood disorders, heart troubles, fever, vomiting, loss of memory, leucoderma, jaundice, tumors, mouth troubles, sore-eye and gonorrhea. In Sri Lanka, the plant is used to cure menorrhagia and profuse phlegm[5]. It is also used for the treatment of bleeding piles[6], impotence and sexual disorders[7].

In order to prepare the respiratory tracts for the rigorous breathing exercises, chewing the leaf buds alone or with a small amount of ginger root is a common yogic practice. Many leaf preparations are used in Southeast Asia to treat leprosy, bleeding, haemorrhage, skin conditions, wounds, and headaches[8,9]. The bruised fresh leaves are used for snake-bites in India and Sri Lanka[10].

Methods and Materials:

The plant leaf extract was prepared by using 25 gm of fresh leaves collected from the local areas. Fresh leaves were washed extensively with water followed by final wash twice thrice with distilled water to remove all the dust and unwanted visible particle. The leaves were cut in to small pieces and then shade dried for 2-3 days. Leaves were homogenized to a fine coarse powder using mortar and pestle and then stored in fine air tight container for further process.

Preparation of Plant Extract:
The powdered dried plant leaves were taken in a round bottom flask and extracted (25g) exclusively with 100 ml each of acetone, methanol, ethyl acetate, chloroform and diethyl ether in a soxhlet extractor for 4 hrs. and few porcelain pieces were added in to it to avoid bumping. After heating gently removed the solvent from sample by evaporation extract remains in round bottom flask used for phytochemical test.

Phytochemical Analysis:
Phytochemical analysis was carried out using standard methods[11,12,13,14].

1) **Test for Carbohydrates :**
   Test for Starch:
   Procedure: Plant extract + 5 ml 5% KOH
   Observation: A canary colouration.
2) **Test for Glycosides :**
   i. **10% NaOH test:**
      Procedure: 1 ml dil. H2SO4+0.2 ml extract+ boiled for 15 min + allowed cooling+ neutralize with 10%NaOH + 0.2 ml feeling solution A and B.
      Observation: A brick red precipitate.
   ii. **Concentrate H_2So_4 test:**
      Procedure: 5ml extracts solution + 2 ml Glacial acetic acid + a drop of 5% $Fecl_3$ + Con. H_2SO_4
      Observation: A brown ring is observed
3) **Test for Proteins and Amino acids :**
   Xanthoproteic test:
   Procedure: Plant extract + few drops of Con. nitric acid.
   Observation: Yellow colored solution.
4) **Salkowski's Test (Detection of Phytosteols):**
   Procedure: plant extract with chloroform + few drops of Conc. H2SO4, (Shake well and allowed to Stand).
   Observation: Formation of Brown Color ring.
5) **Salkowski's Test (Detection of Terpinoids):**
   Procedure :Plant extract + Chloroform + few drops of Conc. H2SO4, Shake well and allowed to Stand.
   Observation: Reddish brown coloration (at bottom).
6) **Test for Alkaloids:**
   i. **Wagner's Test:**
      Procedure: 1 ml Plant extract + 2ml Wagner's reagent (Solution of Iodine in Potassium Iodide)
      Observation: Brown colored ppt. is formed
   ii. **Mayer's test:**
      Procedure: 1 ml plant extract with dil HCL +1-2 drops of mayer's reagent (Potassium mercuri iodide solution) Along the side of test tube.
      Observation: yellow precipitate formed
7) **Test for Flavonoids:**
   Lead acetate Test:
   Procedure: Plant extract is dissolved in 5 ml of distilled water + 3 ml of 10% lead acetate solution
   Observation: A White ppt is formed

8) **Test for Phenol:**
Iodine test:- Procedure: 1 ml extract+ few drops of dil. Iodine solution.
Observation: A red colour present

9) **Test for Saponin:**
Foam test Procedure : 0.5 gm plant extract+ 2 ml water (vigorously shaken)
Observation: Persistent foam for 10 min

Result and Discussion:
The results for the phytochemical analysis of *Justicia adhatoda* plant was shown in Table no.1

Sr. No.	Test		Inference
1.	Test for Caebohydrates (Test For Starch)		+ve
2.	Test for Proteins	Xanthoproteic test	+ve
3.	Test for Phytosteols	Salkowski's Test	+ve
4.	Test for Terpinoids	Salkowski's Test	+ve
5.	Test for Alkaloids	Wagner's Test	+ve
		Mayer's test	+ve
6.	Test for Glycosides	NaOH test	+ve
		Conc. H_2SO_4 test	+ve
7.	Test for Flavonoids	Lead acetate test	+ve
8.	Test for Phenol	Iodine Test	+ve
9.	Test for Saponin	Foam Test	+ve

The result from table no.1 shows that among the analyzed phytochemicals are Carbohydrates, Proteins, Phytosterols, Terpenoids, Alkaloids, Flavonoids, Saponin and Phenols were found present in the ethanolic extract of leaves of *Justicia adhatoda* plant. The medicinal properties of the plants are due to the presence of different phytochemicals which are present in the leaves of the plant.

Conclusion:
From the result, it is concluded that extract of leaves of *Justicia adhatoda* plants contains many active phytochemicals. Therefore the extract of these plants can be used as a drug. Further studies on isolation, purification, and characterization of phytochemicals are suggested for the development of new plant base pharmaceuticals having lesser side effects.

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48

In-Silico Prediction of Phytoconstituents From *Solanum Indicum* for Antistress Activity Targeting Ask 1 Inhibitor

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ABSTRACT

Objective Stress in psychology is defined as tension or pressure on emotion. Natural products and their active principles as sources for new drug discovery and treatment of diseases have attracted considerable attention of researchers. Compounds found in medicinal plants have been the source of many conventional medications. *In-silico* testing of *Solanum indicum* phytoconstituents on ASK 1 inhibitor for antistress efficacy was a part of our investigation.

Methods
Utilizing Discovery studio, molecular docking is done to assess the pattern of interaction between the phytoconstituents from the plant *Solanum indicum* and the crystal structure of the ASK 1 inhibitor (PDB ID: 3VW6). Later, SwissADME and pkCSM were used to screen for toxicity as well as the pharmacokinetic profile. Further, interaction between proteins by STRING network analysis was also evaluated.

Results
The docked results suggest that Solafuranone (-8.4 kcal/mol), Isofraxidin (-6.9 kcal/mol) for 3VW6 macromolecule has best binding towards antistress activity as compared to the standard (Fluvoxamine) for 3VW6 is -6.6 kcal/mol. Furthermore, pharmacokinetics and toxicity parameters were within acceptable limits according to ADMET studies.

Conclusion
Targeting ASK 1 inhibitor against the stress by phytomolecules from *Solanum indicum* can serve as a rational approach for designing future antistress drugs.

KETWORDS*: In-silico***,** *Solanum indicum*, anti-stress activity, 3VW6, Discovery studio.

1. INTRODUCTION

The plant *Solanum indicum*, is a member of the Solanaceae family and is also known as Byakur, Guta started, Kata began and Indian Night Shade. *Solanum indicum*, also known as Badi Bhatkataiya in Hindi and "Brihati" in Sanskrit, is a plant used either alone or in combination with other drugs in the Ayurvedic medicinal system. The use of seeds, roots, leaves, and berries can be used to treat a variety of illnesses, including bronchitis, asthma, dry cough, rhinitis, dysuria, leucoderma, sexual dysfunction, insomnia, weak heartbeat, and pruritis.[1]

A prickly perennial under shrub that can reach a height of 1 m and is mostly found in warmer areas of India up to a height of 1500 m, *Solanum indicum*, sometimes known as poison berries in English, is recognised for its poisonous berries-like fruit. This important medicinal plant is frequently used to treat poisonous affections, skin diseases, ulcers, breathing difficulties, abdominal pain, cough, and dyspepsia in folk and traditional Indian systems of medicine. Siddha and Ayurveda both use it.[2]

However, there are few studies on the phytoconstituents of *Solanum indicum* for the antistress activity. Thus, keeping the above information in view, the present investigation was designed to identify the potential phytochemicals of *Solanum indicum* against 3VW6 using a molecular docking method.

2. MATERIALS AND METHODS

2.1. Platform for molecular docking

The computational docking study of all the phytoconstituents selected as ligands with antistress activity as the target was performed using PyRx software.[3]

2.2. Protein preparation

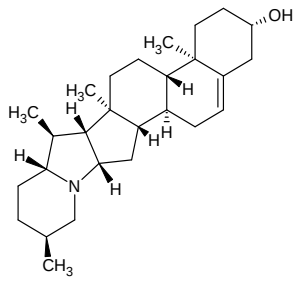
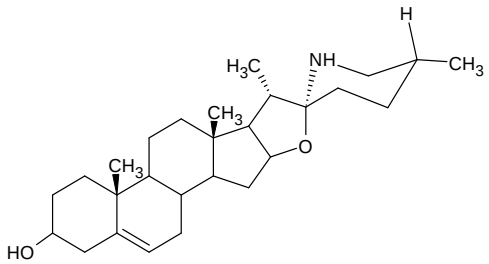
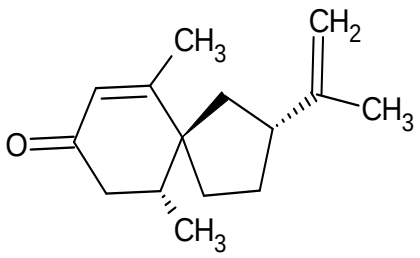
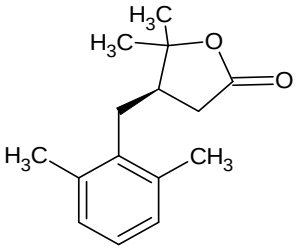
The macromolecule is 3VW6, *in silico* analysis of selected phytoconstituents was performed on the 2.40 Å crystal structure of antistress macromolecule with inhibitor, (PDB ID: 3VW6, having resolution Resolution: 2.40 Å, R-Value Free: 0.252, R-Value Work: 0.213, R-Value Observed: 0.215), which was retrieved from the protein data bank (https://www.rcsb.org). 3VW6 is classified as Crystal structure of human apoptosis signal-regulating kinase 1 (ASK1) with imidazopyridine inhibitor all other molecules, such as co-crystallized water molecules, unwanted chains, and nonstandard residues, were deleted. Using Discovery studio.[4]

2.3. Mechanism of Action

3VW6: Apoptosis signal-regulating kinase 1 (ASK1) was originally identified as a member of the mitogen-activated protein kinase (MAP3K) family that activates both p38 MAP kinase and c-Jun N-terminal kinase (JNK) pathways ASK1 is stimulated by various cell stressors including cytotoxic cytokines, reactive oxygen species (ROS), and endoplasmic reticulum stress. Recent studies revealed that ASK1 contributes not only to the regulation of cell death, but also to cytokine responses, cell differentiation, and immune regulation. Therefore, ASK1 inhibitors are thought to have potential for the protection of cells from various stresses in wide-ranging pathological situations such as autoimmune disease, diabetes, cardiovascular disease, neurodegenerative disorders, and inflammatory disorders.[5]

2.4. Ligand preparation

The three-dimensional (3D) structures of all constituents were retrieved using Avogadro software from the PubChem database available on the NCBI website (https://pubchem.ncbi.nlm.nih.gov/). However, the drawing of geometrical 2D structure was performed using the ChemSketch program. The two-dimensional (2D) structures were transformed into 3D models using the Avogadro software and the ligand structures were saved in the PDB format. All the chemical structures are shown in Figure 1.

Solanidine 	Solasodine 
Solavetivone 	Solafuranone 

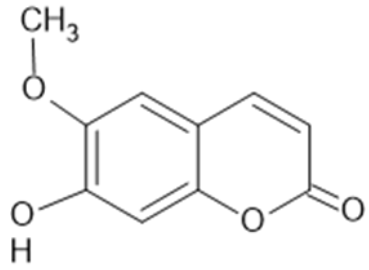
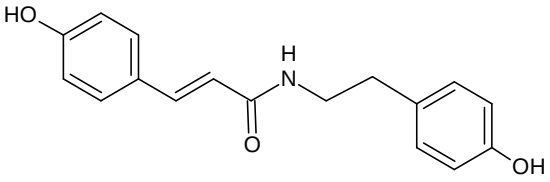
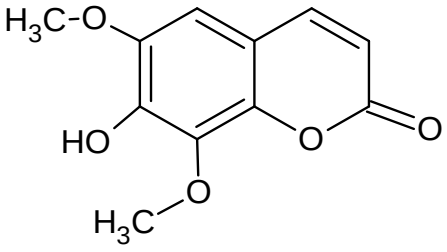
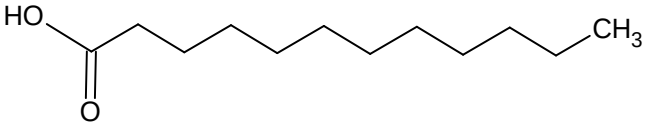
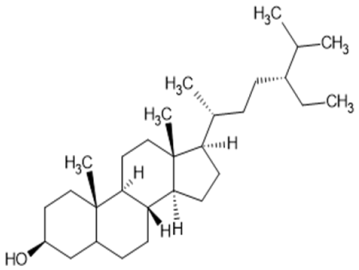
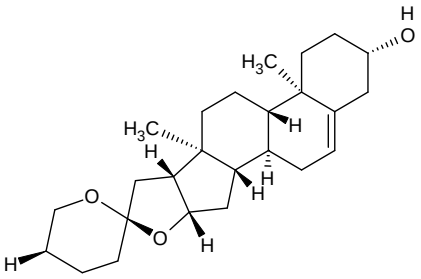
Scopoletin 	N-p-trans-Coumaroyltyramine 
Isofraxidin 	Lauric acid 
β-sitosterol 	Diosgenin 

Fig. 1. Chemical structures of all selected phytoconstituents in the molecular docking studies

2.5. Standard Preparation

The standard is prepared steps such as, the 2D structure of standard drug was made using chem sketch program, then the 2D structure was converted into 3D model using Avogadro Software, it was saved in PDB format.

By using PyRx molecular docking of Fluvoxamine was done with 3VW6.

2.6. Molecular docking

Molecular docking evaluates the protein-ligand interactions and estimates the scoring function based on the geometry to predict the binding affinity of the ligand molecule[6,7]. We applied molecular docking studies to investigate the binding pattern of selected phytoconstituents (Figure 1) and the standard drug, along with the crystal structure of antistress activity macromolecule (PDB ID: 3VW6). The molecular docking study was performed using PyRx software, Binding affinity was explored using the Vina wizard tool. The final results were analysed and visualized using Discovery Studio 2020 Client [8], with bound ligands as the

standard. Visualization of protein ligand interaction reflects the number of interactions and active residues responsible for significant binding at the active site of the target enzyme.

2.7. Absorption, distribution, metabolism, and excretion (ADME) and toxicity prediction

The selected phytoconstituents and standard drug were further checked for drug-likeness properties according to Lipinski's rule. During drug development, it is necessary to predict the tolerability of phytochemicals before being ingested by humans and animal models. The pharmacokinetic profile (ADME) and toxicity predictions of ligands were conducted using SwissADME (http://www.swissadme.ch) and pkCSM (an online server database predicting small-molecule pharmacokinetic properties using graph-based signatures, (http://biosig.unimelb.edu.au/pkcsm/prediction). To analyse the toxicological properties of ligands, Simplified Molecular Input Line Entry System (SMILES) notations or PDB files were uploaded, followed by selecting the required models for generating numerous information about structure-related effects[9,10].

3. RESULT AND DISCUSSION

The present study aimed to explore the inhibitory potential of the phytoconstituents present in *Solanum indicum* targeting antistress activity. In this study, we performed molecular docking studies of all phytoconstituents found in *Solanum indicum* using AutoDock Vina, followed by a study of interacting amino acid residues and their influence on the inhibitory potentials of the active constituents. Selected phytoconstituents showing the best fit were further evaluated for absorption, distribution, metabolism, excretion, and toxicological (ADMET) properties using SwissADME and pkCSM servers.

3.1 Molecular docking

The docking scores and binding energies of all chemical constituents of *Solanum indicum* targeting antistress activity (PDB ID: 3VW6) and binding interactions with amino acid residues are presented in Table 1 respectively.

Table 1. Binding interaction of ligands from *Solanum indicum* targeting antistress activity (PDB ID:3VW6)

Sr. No.	Chemical constituent	PubChem ID	Docking Score
			3VW6
1.	Solanidine	65727	-9.1
2.	Solasodine	5250	-7.4
3.	Solavetivone	442399	-6.9
4.	Solafuranone	11107208	-8.4
5.	Scopoletin	5280460	-6.7
6.	N-p-trans-Coumaroyltyramine	5372945	-7.0
7.	Isofraxidin	5318565	-6.9
8.	Lauric acid	3893	-3.7
9.	β-sitosterol	222284	-7.4
10.	Diosgenin	99474	-8.5
Standard Drug			
11	Fluvoxamine	5324346	-6.6

The binding affinities of phytoconstituents ranged from –9.1 to −3.7 kcal/mol. From the docked results, it is evident that the compounds, Solanidine exhibit the most favourable binding affinity (−9.1 kcal/mol) in complex with selected macromolecules (PDB ID: 3VW6) as compared to other docked compounds i.e., Diosgenin (−8.5 kcal/mol), Solafuranone (−8.4 kcal/mol), Solasodine (−7.4 kcal/mol), Beta sitosterol (-7.4 kcal/mol), N-p-trans-

Coumaroyltyramine (−7.0 kcal/mol), Isofraxidin (−6.9 kcal/mol), Solavetivone (−6.9 kcal/mol), Scopoletin (−6.7 kcal/mol), Lauric acid (−3.7 kcal/mol). Visual examination of the computationally docked optimal binding poses of phytoconstituents on selected macromolecules (i.e., 3VW6) revealed the significant involvement of various types of interactions, such as hydrogen bonding and hydrophobic interactions, including π–π stacking and π–alkyl and alkyl interactions, in the stability of the binding of the phytoconstituents to 3VW6.

The binding affinity of the standard (Fluvoxamine) for 3VW6 is -6.6 kcal/mol.

3.1.1. Solafuranone, 3VW6

The number of intermolecular hydrogen bonds, the binding energy of ligand-3VW6 stable complexes, and the number of nearest amino acid residues were also determined for selected compound Solafuranone. All synthesized derivatives formed complexes with target proteins. Analysis of interactions of the 3VW6 protein complex and ligand Solafuranone showed that the ligand molecule is oriented due to Pi-alkyl interactions with LEU A: 810 amino acid residues Conventional Hydrogen bond with LYS A: 709 and Pi-Sigma interaction with LEU A: 686 amino acid residue were found.

3.1.2. Isofraxidin, 3VW6

An analysis of the interactions between the 3VW6 protein complex and the Isofraxidin ligand was also carried out, which showed that the ligand molecule is oriented due to conventional hydrogen bond with the amino acid residue LYS A: 688 and SER A: 821 and Pi-Alkyl and Alkyl interaction with ALA A:707, LUE A:686 and LUE A: 810, Pi-Sigma interaction with VAL A: 694 amino acid residue were found.

3.1.3. Fluvoxamine, 3VW6

The binding affinity of the standard (Fluvoxamine) for 3VW6 is -6.6 kcal/mol. the interactions between the 3VW6 protein complex and the Fluvoxamine ligand was also carried out, which showed that the ligand molecule is oriented due to conventional hydrogen bond with the ASP A:803, ARG A:767, SER A:821 amino acid residue, Pi-Alkyl and Alkyl interaction with ALA A:7047, MET A:754, LEU A:810, VAL A:694 amino acid residue and Salt bridge with ASP A:822 amino acid residue were found.

Table No. 2. Interaction with amino acid residue.

Sr. No.	Molecule	Binding Energy (kcal/mol)	H bond	Main amino acid interactions	
				Pi-alkyl, alkyl, Pi-S/Pi-Pi, T shaped/halogen/unfavourable donor-donor interactions	Van der Waals interactions
1	Solanidine	-9.1	No interaction	PHE A: 782, TRP A: 770	No interaction
2	Solasodine	-7.4	ASN A: 702, ASP A: 699	LEU A: 741, VAL A: 704, ARG A: 705	No interaction

3	Solavetivone	-6.9	No interaction	LEU A: 810, VAL A: 694	No interaction
4	Solafuranone	-8.4	LYS A: 709	LEU A: 810, LEU A: 686	No interaction
5	Scopoletin	-6.7	VAL A: 757, GLU A: 755, LYS A:709	MET A: 754, LEU A: 810, VAL A: 694, ALA A: 707, LEU A: 686	No interaction
6	N-p-trans-Coumaroyltyramine	-7.0	VAL A: 757	GLY A: 759, VAL A: 694, MET A: 754	No interaction
7	Isofraxidin	-6.9	LYS A: 688, SER A: 821	ALA A: 707, LEU A: 686, LEU A: 810, VAL A: 694	No interaction
8	Lauric acid	-3.7	GLN A: 756	LEU A: 810	No interaction
9	β-sitosterol	-7.4	No interaction	LEU A: 686, ALA A: 707, MET A: 754, LEU A: 810, VAL A: 738, VAL A: 694, VAL A: 685, LYS A: 688	No interaction
10	Diosgenin	-8.5	ASN A: 702	ARG A: 705, VAL A: 704	No interaction
11	Fluvoxamine	-6.6	ASP A: 803, ARG A: 767, SER A: 821	ASP A: 822, VAL A: 694, LEU A: 810, MET A: 754, ALA A: 707	No interaction

3.2. ADMET study

Pharmacokinetic profile (ADME) and toxicity predictions of the ligands are important attentive parameters during the transformation of a molecule into a potent drug. In the present study, these parameters were assessed using SwissADME and pkCSM. The absorption potential and lipophilicity are characterized by the partition coefficient (Log *P*) and topological polar surface area (TPSA), respectively. For better penetration of a drug molecule into a cell membrane, the TPSA should be less than 140 Å. However, the value of Log *P* differs based on the drug target. The ideal Log *P* value for various drugs are as follows: oral and intestinal absorption, 1.35 − 1.80; sublingual absorption, > 5; and central nervous system (CNS)[11]. The aqueous solubility of ligands ideally ranges from − 6.5 to 0.5 [12], while the blood brain barrier (BBB) value ranges between − 3.0 and 1.2 [13]. In addition, non-substrate P-glycoprotein causes drug resistance [14].

In our study, all the selected ligands followed the TPSA parameter, P-glycoprotein non-inhibition, thereby showing good intestinal absorption and an acceptable range of BBB values. All the compounds showed aqueous solubility values within the range. Further, it was predicted that the selected ligands do not show AMES toxicity, hepatotoxicity, and skin sensitivity. In addition, it did not inhibit hERG-I (low risk of cardiac toxicity). Lipinski's rule violations, *T. pyriformis* toxicity, minnow toxicity, maximum tolerated dose, rat acute oral toxicity, and chronic toxicity are depicted in table.

Table 3. ADME and toxicity predicted profile of ligands with superior docking score

ADMET Properties	Formula	MW (g/mol)	Log P	TPSA (Å^2)	HB donor	Hb acceptor	Aqueous solubility (Log mol/L)	Human intestinal absorption (%)	Blood Brain Barrier
Solanidine	$C_{27}H_{43}NO$	397.647	5.655	23.47 Å^2	1	2	-4.927	92.975	0.695
Solasodine	$C_7H_{43}NO_2$	413.64	5.2869	41.49 Å^2	2	3	-3.809	92.324	0.035
Solavetivone	$C_{15}H_{22}O$	218.33	3.9042	17.07 Å^2	0	1	-4.615	95.873	0.635
Solafuranone	$C_{15}H_{20}O_2$	232.323	3.18764	26.30 Å^2	0	2	-3.551	95.523	0.206
Scopoletin	$C_{10}H_8O_4$	192.17	1.5072	59.67 Å^2	1	4	-2.504	95.277	-0.299
N-p-trans-Coumaroyltyramine	$C_{17}H_{17}NO_3$	283.327	2.4699	69.56 Å^2	3	3	-3.165	90.031	-0.552
Isofraxidin	$C_{11}H_{10}O_5$	222.196	1.5158	68.90 Å^2	1	5	-2.458	95.588	-0.377
Lauric acid	$C_{12}H_{24}O_2$	200.322	3.9919	37.30 Å^2	1	1	-4.181	93.379	0.057
β-sitosterol	$C_{29}H_{50}O$	414.718	8.0248	20.23 Å^2	1	1	-6.773	94.464	0.781
Diosgenin	$C_{27}H_{42}O_3$	414.63	5.7139	38.69 Å^2	1	3	-5.713	96.565	0.2

Fluvoxamine	$C_{15}H_{21}F_3N_2O_2$	318.339	3.2015	56.84 Å^2	1	4	-3.641	90.686	-0.312

Table 3 Continued

ADMET Properties	P-glyco-protein substrate	Total clearance [Log mL/ (min.kg)]	Bioavailability score score	AMES toxicity	Max tolerated dose [Log mg/ (kg.d)]	hERG I inhibitor	hERG II inhibitor
Solanidine	YES	0.028	0.55	NO	-0.882	NO	YES
Solasodine	YES	0.09	0.55	NO	-0.375	NO	YES
Solavetivone	NO	1.225	0.55	NO	0.044	NO	NO
Solafuranone	NO	1.256	0.55	NO	0.526	NO	NO
Scopoletin	NO	0.73	0.55	NO	0.614	NO	NO
N-p-trans-Coumaroyltyramine	YES	0.265	0.55	NO	-0.213	NO	YES
Isofraxidin	NO	0.713	0.55	NO	0.56	NO	NO
Lauric acid	NO	1.623	0.85	NO	-0.34	NO	NO
β-sitosterol	NO	0.628	0.55	NO	-0.621	NO	YES
Diosgenin	NO	0.328	0.55	NO	-0.559	NO	YES
Fluvoxamine	NO	0.589	0.55	NO	0.213	NO	YES

Table 3 Continued

ADMET Properties	Acute oral rat toxicity. LD50(mol/kg)	Oral rat chronic toxicity (Log mg/kgbw/day)	Hepatotoxicity	Skin sensation	T.Pyriformis toxicity (Log µg/L)	Minnow toxicity (Log mmol/L)	Lipinski's rule Violation

Solanidine	2.596	1.334	YES	NO	0.378	-0.493	YES (1)
Solasodine	2.489	1.332	YES	NO	0.311	0.381	YES (1)
Solavetivone	1.643	1.19	NO	YES	1.453	0.874	YES (0)
Solafuranone	1.865	1.947	NO	YES	2.151	0.557	YES (0)
Scopoletin	1.95	1.378	NO	NO	0.516	1.614	YES (0)
N-p-trans-Coumaroyltyramine	2.17	1.271	NO	NO	1.008	1.514	YES (0)
Isofraxidin	2.326	1.825	NO	NO	0.431	1.862	YES (0)
Lauric acid	1.511	2.89	NO	YES	0.954	-0.084	YES (0)
β-sitosterol	2.552	0.855	NO	NO	0.43	-1.802	YES (1)
Diosgenin	1.921	1.452	NO	NO	0.399	0.247	YES (1)
Fluvoxamine	3.311	1.314	NO	NO	1.183	0.841	YES (0)

3.3. Interaction of Standard Drug (Fluvoxamine) with 3VW6

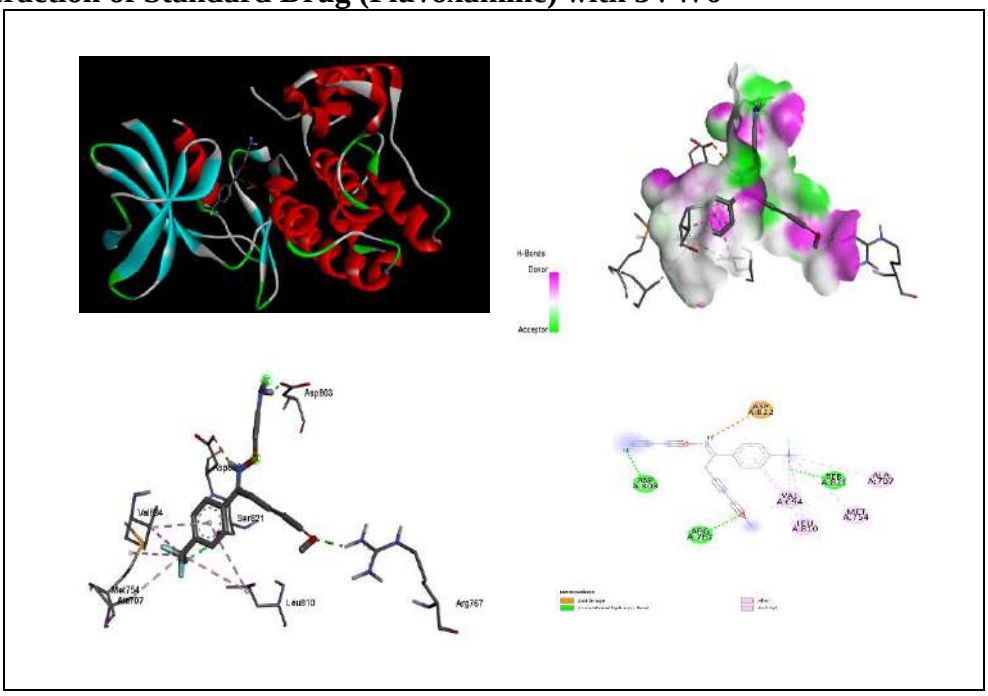
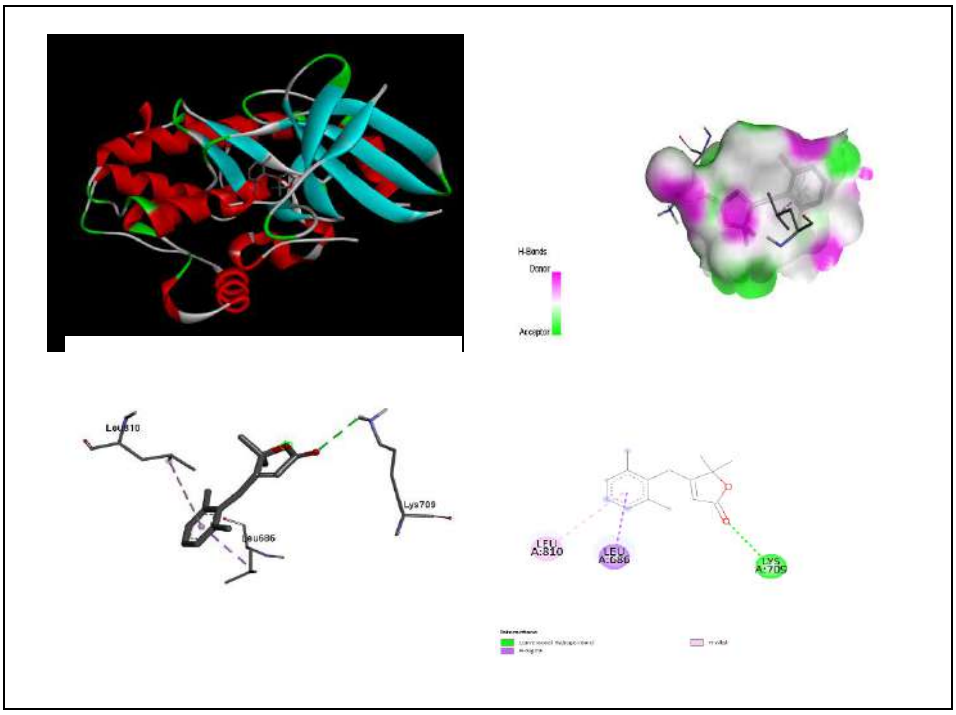


Fig. 2. Docking scores and binding interaction of Fluvoxamine (PDB ID: 3VW6). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

3.4. Interactions of phytoconstituents with 3VW6

A.Solafuranone



B.Isofraxidin

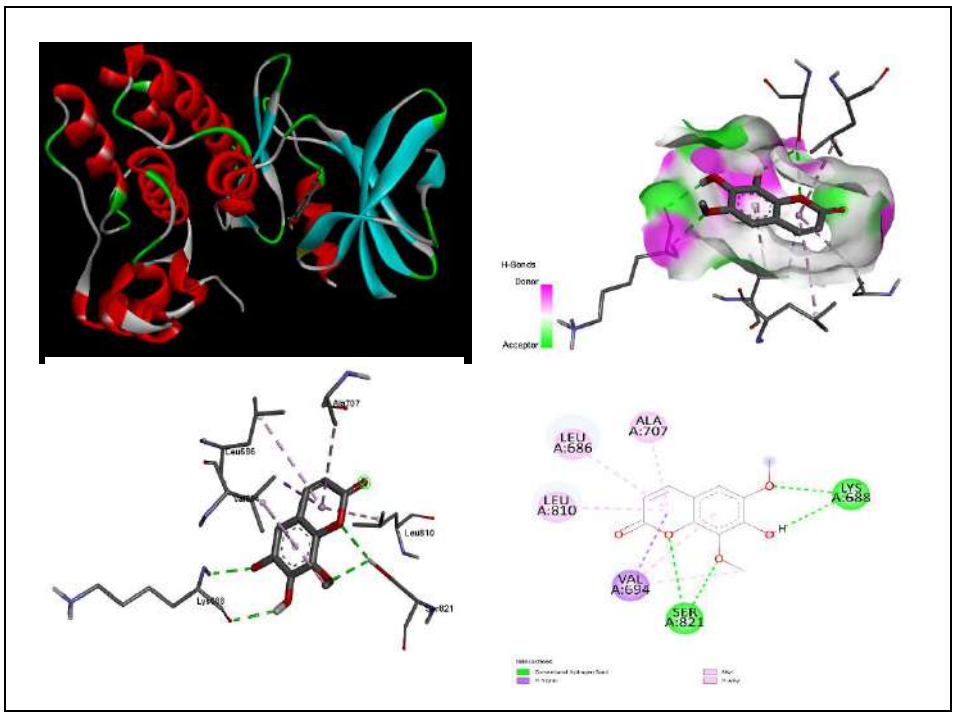


Fig. 3. Docking scores and binding interaction of phytoconstituents (PDB ID: 3VW6). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

3.5. Boiled Egg

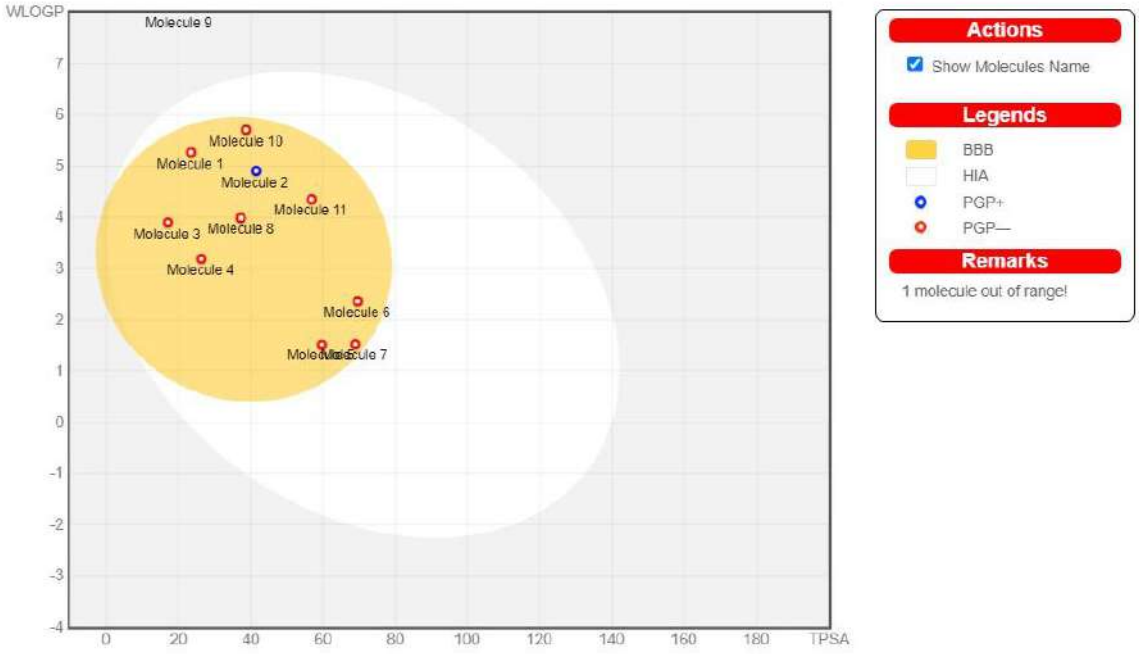


Fig no. 4. Combined Boiled Egg Diagram

Table no. 4. Name of molecules contained in Boiled Egg Diagram

MOLECULE NUMBER	MOLECULE NAME
1	Solanidine
2	Solasodine
3	Solavetivone
4	Solafuranone
5	Scopoletin
6	N-p-trans-Coumaroyltyramine
7	Isofraxidin
8	Lauric acid
9	β-sitosterol
10	Diosgenin
11	Fluvoxamine

BOILED means **B**rain **O**r **I**ntestina**L** **E**stimate**D** permeation predictive model. The boiled egg diagram shows two regions white region and yellow region.

The white region is the physicochemical space of molecules with highest probability of being absorbed by the gastrointestinal tract, and the yellow region (yolk) is the physicochemical space of molecules with highest probability to permeate to the brain.

In addition, the points are coloured in blue if predicted as actively effluxed by P-gp (PGP+) and in red if predicted as non-substrate of P-gp (PGP-).

4. CONCLUSION

In this study, we have carried out an *in-silico* screening of the phytoconstituents of *Solanum indicum* plant. This study demonstrated the sixteen compounds from *Solanum indicum* plant, (Solanidine, Solasodine, Solavetivone, Solafuranone, Scopoletin, N-p-trans-Coumaroyltyramine, Isofraxidin, Lauric acid, β-sitosterol, Diosgenin). The selected phytocompounds showed docking scores ranging from –9.1 to −3.7 kcal/mol in 3VW6. Among all, Solafuranone and Isofraxidin gave the highest binding energy (−8.4 kcal/mol) and (−6.9

kcal/mol) in complex with 3VW6, whereas the reference compound, Fluvoxamine showed a docking score with a binding energy of -6.6 kcal/mol. Furthermore, these ligands exhibited good ADMET properties. To summarize, phytoconstituents present in *Solanum indicum* possess strong effects against 3VW6 and could be further evaluated for their antistress effect, as well as for the development of alternative drugs with fewer side effects for the treatment of stress.

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49

Design, Synthesis, Spectral Characterisation and Antibacterial Screening of Some Novel 4-Substitutedimino-1,3,5-Dithiazine Along With Pyrimidine Nucleus

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ABSTRACT

In recent times in the laboratory, synthesis of 2-(2-Phenylimino-4-substitutedimino-1,3,5-dithiazino) aminopyrimidine **(IIIa-e)** were synthesized by refluxing 2-(5-phenyl-2,4-dithiobiureto) pyrimidine **(I)** with alkyl/arylisocyanodichlorides **(IIa-e)** in acetone-ethanol medium in 1:1 molar proportion. The structures of all the synthesized compounds were acceptable on the basis of chemical characteristics, elemental analysis, spectral studies and their antibacterial screening against the gram positive and gram negative bacteria such as *S. typhi, E. coli, S. aureus, A. Aerogenes, B. Subtilis* and *B. Megatherium.etc.*

INTRODUCTION

Heterocycles containing organic molecules are more fascinating, because they are convenient in a variety of applications, a multitude of uses are included by the heterocycles' size and heteroatom diversity. These compound nitrogen, oxygen and sulphur are composed of six member[1-5], five member[6-7] fused heterocycles with aromatic rings. Particularly noteworthy are the numerous biological and industrial uses for heterocycles that combine sulphur and nitrogen in one ring. Six member two sulphur and one nitrogen atom prepare 1,3,5-dithiazine. It is one of the six member heterocycles that functions as a strong medication in the sectors of medicine, agriculture, and industry[9-8].

Tayade[10], Pathe[11] and Mur[12] Synthesized numerous heterocycles containing 1,3,5-dithiazines as main nucleus. Each 1,3,5-dithiazino moiety has different applications according to the substituent attached to the basic nucleus of the 1,3,5-dithiazine. It has been also observed during literature study that, 1,3,5-dithiazino nucleus and its derivatives possesses biological and medicinal effective properties[13-14].

Substituted isocyanodichlorides were used by researchers to synthesise 1,3,5-dithiazines in the laboratory. This 1,3,5-dithiazine synthesis technique is quicker, less complicated, less expensive and requires less time.

MATERIAL AND METHOD

Material

All the chemical used were of loba chemie (AR grade).

Method

In the present experiment for the synthesis of different substituted 1,3,5-dithiazino aminopyrimidine is conventional refluxing under electronic water bath for different hours for different experiment**.**

EXPERIMENTAL

All the chemicals used for the synthesis were purified. After refluxing the purity of the compounds were checked by TLC (aluminium TLC) with thin layer thickness of 200 um. The melting points of all synthesize compounds will be recorded using hot paraffin bath. The carbon and hydrogen analysis were carried out on Carlo-Ebra-1106 analyser Nitrogen estimation were carried out with colmon-N-analyzer-29. IR spectra were recorded with Bruker spectrometer in

the range 4000-400 cm-1. PMR spectra were recorded on VARIAN 400 MHz spectrometer with TMS as internal standard using $CDCL_3$ and DMSO Solvent.

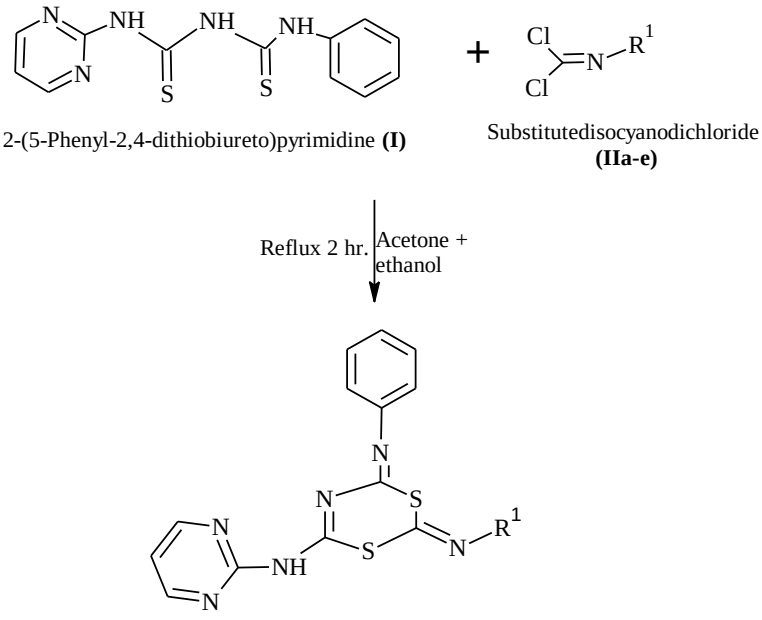
GENERAL PROCEDURE

A reaction of 2-(5-phenyl-2,4-dithiobiureto)pyrimidine **(I)** and substitute disocyanodichloride **(IIa-e)** in 1:1 molar ratio refluxed on water bath in acetone-ethanol medium for 2 hours. The evolution of the hydrochloride gas was clearly observed during refluxtion. After distillation of excess solvent orange product isolated which on basification with dilute ammonium hydroxide orange crystalline products obtained.

Similar, procedure was adopted for the synthesis of all the derivatives in the series.

The tentative reaction for the formation of product is depicted below,

Reaction



2-(5-Phenyl-2,4-dithiobiureto)pyrimidine **(I)**

Substitutedisocyanodichloride **(IIa-e)**

2-(2-Phenylimino-4-substitutedimino-1,3,5-dithiazino)aminopyrimidine

(IIIa-e)

Similarly, 2-(5-phenyl-2,4-dithiobiureto)pyrimidine **(I)** were react with phenylisocyanochloride **(IIa),** ethylisocyanodichloride **(IIb),** tertbutylisocyanodichloride **(IIc**), P-tolylisocyanodichloride **(IId**) and 4-chlorophenhylisocyanodichloride (**IIe)** by the above mentioned method to isolate 2-[2,4-di(phenylimino)-1,3,5-dithiazino] aminopyrimidine **(IIIa)**, 2-(2-phenylimino-4-ethylimino-1,3,5-dithiazino) aminopyrimidine**(IIIb)**, 2-(2-phenylimino-4-*tert*-butylimino-1,3,5-dithiazino) aminopyrimidine **(IIIc)**, 2-[2-phenylimino-4-(4-methylphenylimino)-1,3,5-dithiazino]aminopyrimidine **(IIId)** and 2-[2-phenylimin-4-(4-chlorophenylimino)-1,3,5-dithiazino]aminopyrimidine **(IIIe).**

RESULT AND DISCUSSION

Spectral characterization results for all the synthesized compounds are given below

Spectral Characterization

1. 2-(2,4-diphenylimino-1,3,5-dithiazino)aminopyrimidine (IIIa)

Colour-Yellow solid, **Molecular formula**- $C_{15}H_{14}N_6S_2$, **Yield** 85%, **M.P**. 162^0C, **% Composition found (calculated)** C-52.90 , H-4.83 , N-25.20, S-23.21 , **FTIR (Kbr) vcm**-3245.22 N-H stretching, 3051.47 (C-H Ar Stretching), 3187.38 (N-H Amido), 1950.37 (C-H Ar Bending,), 1185.99 (C=S Stretching), 670.04(=C-H bending); **1H NMR (400MHz $CDCL_3$ δ ppm)**, 8.4ppm (2H, double, CH) of pyrimidine, 7.2ppm (2H, CH, doublet) of pyrimidine, 7.2

ppm (2H, , doublet CH) of phenyl, 3.4 ppm (1H, singlet NH), 4.6 ppm 1H singlet, 7.39 1H triplet CH benzene, 1H triplet CH benzene 2.2 ppm 2H quartet, 2.3 ppm 3H triplet **Mass** m/z 390.30

2. 2-(2-phenylimino-4-ethylimino-1,3,5-dithiazino)aminopyrimidine (IIIb)

Colour-Yellow solid, **Molecular formula**- $C_{15}H_{14}N_6S_2$, **Yield** 86%, **M.P**. 170^{0}C, **% Composition found (calculated)** C-52.90 , H-4.83 , N-25.20, S-23.21 , **FTIR (Kbr) vcm**-3245.22 N-H stretching, 3051.47 (C-H Ar Stretching), 3187.38 (N-H Amido), 1950.37 (C-H Ar Bending,), 1185.99 (C=S Stretching), 670.04(=C-H bending); **1H NMR (400MHz CDCL$_3$ δ ppm)**, 8.4ppm (2H, double, CH) of pyrimidine, 7.2ppm (2H, CH, doublet), 7.2 ppm (2H, , doublet CH) of phenyl, 3.4 ppm (1H, singlet NH), 4.6 ppm 1H singlet, 7.39 1H triplet CH benzene, 1H triplet CH benzene 2.2 ppm 2H quartet, 2.3 ppm 3H triplet **Mass** m/z 342.30

3. 2-(2-phenylimino-4-tertbutylimino-1,3,5-dithiazino)aminopyrimidine (IIIc)

Colour-Yellow solid, **Molecular formula**- $C_{17}H_{18}N_6S_2$, **Yield** 90%, **M.P**. 158^{0}C, **% Composition found (calculated)** C-55.90 , H-4.83 , N-23.20, S-17.21 , **FTIR (Kbr) vcm**-3245.22 N-H stretching, 3045.47 (C-H Ar Stretching), 3140.38 (N-H Amido), 1995.37 (C-H Ar Bending,), 1164.99 (C=S Stretching), 710.04(=C-H bending); **1H NMR (400MHz CDCL$_3$ δ ppm)**, 8.2ppm (2H, double, CH), 7.2ppm (2H, CH, doublet), 7.1ppm (2H, , doublet CH), 3.5 ppm (1H, singlet NH), 4.5 ppm 1H singlet, 7.40 1H triplet CH benzene, 2.4 9H singlet **Mass** m/z 370.50

4. 2-(2-phenylimino-4-tolylimino-1,3,5-dithiazino)aminopyrimidine (IIId)

Colour-Yellow solid, **Molecular formula**- $C_{20}H_{16}N_6S_2$, **Yield** 82%, **M.P**. 167^{0}C, **% Composition found (calculated)** C-55.90 , H-4.83 , N-23.20, S-15.21 , **FTIR (Kbr) vcm**-3200.22 N-H stretching, 2901.47 (C-H Ar Stretching), 316038 (N-H Amido), 1960.37 (C-H Ar Bending,), 1167.99 (C=S Stretching), 745.04(=C-H bending); **1H NMR (400MHz CDCL$_3$ δ ppm)**, 8.2 ppm (2H, double, CH) of pyrimidine, 7.3ppm (2H, CH, doublet), 7.2 ppm (2H, , doublet CH), 3.5 ppm (1H, singlet NH), 4.7 ppm 1H singlet, 7.39 1H triplet CH benzene, 3.4 ppm 3H singlet. **Mass** m/z 404.60

5. 2-(2-phenylimino-4-p-chlorophenylimino-1,3,5-dithiazino)aminopyrimidine (IIIe)

Colour-Yellow solid, **Molecular formula**- $C_{19}H_{13}N_6S_2$, **Yield** 80%, **M.P**. 145^{0}C, **% Composition found (calculated)** C-53.90 , H-3.83 , N-20.20, S-15.21Cl-8.45 , **FTIR (Kbr) vcm**- 3263.22 N-H stretching, 3051.47 (C-H Ar Stretching), 3216.38 (N-H Amido), 1966.37 (C-H Ar Bending,), 1165.99 (C=S Stretching), 720.04(=C-H bending); **1H NMR (400MHz CDCL$_3$ δ ppm)**, 8.4 ppm (2H, double, CH) of pyrimidine, 7.03ppm (2H, CH, doublet), 7.4 ppm (2H, , doublet CH), 3.5 ppm (1H, singlet NH), 4.6 ppm 1H singlet, 7.39 1H triplet CH benzene, **Mass** m/z 424.80.

CONCLUSION

In the present work is cheaper and less time consuming method for synthesis of organic compound (IIIa-e). In all the synthesized compounds give the maximum yield of product (III a-e). A variety of pyrimidine based 1,3,5-dithiazine derivative can be synthesized for their antimicrobial activities adopting the method.

PHARMACOLOGICAL STUDIES

Antimicrobial activity

All the synthesized compounds **(III-a)** to **(III-e)** were screened for antibacterial activity against *S. typhi, E. coli, S. aureus, A. Aerogenes, B. Subtilis* and *B. Megatherium.* by disc diffusion method was performed using mueller hinton agar as well as nutrient agar medium. Each and every compound was tested at conc. 50 μg/ml in ethanol. The zone of inhibition of all the synthesized compounds were measured after 24 hour incubation at 37 ^{0}C. Standard drug used for comparison the activity was Ciprofloxacin.

Table 1: Synthesized compound **IIIa-e** activity against Gram +ve and Gram -ve bacteria

Table No. 1.1 - Antibacterial activity of synthesized compound against bacteria (Zone of inhibition in mm) (after 24 hrs at 37 ºC temp)

SR No.	Compd.	Gram positive			Gram negative		
		S. aureus	***B. subtilis***	***B. megatherium***	***S. typhi***	***E. coli***	***A. aerogenes***
1	**SBS-IIIa**	18	12	16	14	18	11
2	**SBS-IIIb**	11	12	14	14	11	12
3	**SBS-IIIc**	11	11	12	11	11	11
4	**SBS-IIId**	10	12	12	12	11	11
5	**SBS-IIIe**	14	12	14	12	16	12
6	**Std Ciprofloxacin**	18	16	20	18	20	14

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50

Comparative Account of Partial Molar Volumes and Compressibilities of Aqueous-(L-Arginine + Glucose/Lactose) Solutions at 310.15 K

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Abstract: Partial molar volumes and compressibilities of aqueous-(L-Arginine + Glucose/Lactose) solutions have been determined from measured densities and ultrasonic velocities at 310.15 K. The measured, calculated and graphically determined properties viz. densities and ultrasonic velocities, apparent molar volumes and compressibilities and partial molar volumes and compressibilities and have been interpreted in terms of different interactions in studied solutions. Effect of Glucose/Lactose on structural orientation, hydration behavior and different interactions including hydrogen bonding has been evaluated. Study has importance in amino acid-sugar interactions.

Introduction:

L-Arginine is an essential basic amino acid found in protein rich food and strongly interacts with organic acids as well as carbohydrates through hydrogen bonding and hydrophilic/hydrophilic interactions. Glucose is a most abundant monosaccharide sugar [1-2]. Lactose (milk sugar) is a disaccharide sugar used in the food industry [3].

Numbers of researchers have carried out molecular interaction studies of L-Arginine in aqueous and various cosolutes including drug [4-8] solutions. These interactions lead to the perturbation of structure and orientation of aqueous L-Arginine. Sugar interactions with amino acid specifically L-Arginine through volumetric and ultrasonic studies in solution is lacking. In view of importance of these studies in this short communication, we report comparison of partial molar volumes and compressibilities of these solutions at 310.15 K.

Experimental:

L-Arginine (Himedia, 174.2 g/mol) solutions in water and aqueous Glucose (Himedia, 180.16 g/mol)/Lactose (Himedia, 342.30 g/mol) were prepared in double distilled water. Details of experimental work (measurement of densities and ultrasonic velocities) are explained in our previous papers [9-11]. Apparent and partial molar volume and compressibility and corresponding transfer properties are determined using standard relations [12-17].

Results and discussion:

It is seen from Figure 1 and 2 that the measured densities (ρ) and ultrasonic velocities u increase with increase in the concentration of L-Arginine as well as increase in the concentration of cosolutes (Figure 1 A and C, 2 A and C). The apparent molar volumes ($V_{2,\varphi}$) and compressibilities ($\kappa_{2,\varphi}$) increase with increase in concentration L-Arginine as well as increase in cosolute concentration (Figure 1 B and C, 2 B and D). However these values are larger in Lactose solution compared to Glucose solution. This is attributed to the more number of –OH groups in Lactose compared to Glucose which makes loose structure, expansion in volume of hydration with more compression in Lactose.

The partial molar properties, partial molar volumes ($V^0_{2,\phi}$) and partial molar compressibilities ($\kappa^0_{S,2,\phi}$) are determined from straight line equations as an intercept of lines using Masson's and Gucker's equations and solute-solute interaction parameters (S_v and S_k) are determined as a slope of these lines and are listed in Table 1 and 2. Partial molar properties and transfer properties ($\Delta_t V^o_{2,\phi}$ and $\Delta_t \kappa^0_{S,2,\phi}$) of L-Arginine increases on addition of cosolutes and further increases with their concentration. This is due

to the overlap of cospheres of solute and cosolute and release of water molecules into the bulk solution (Scheme 1).

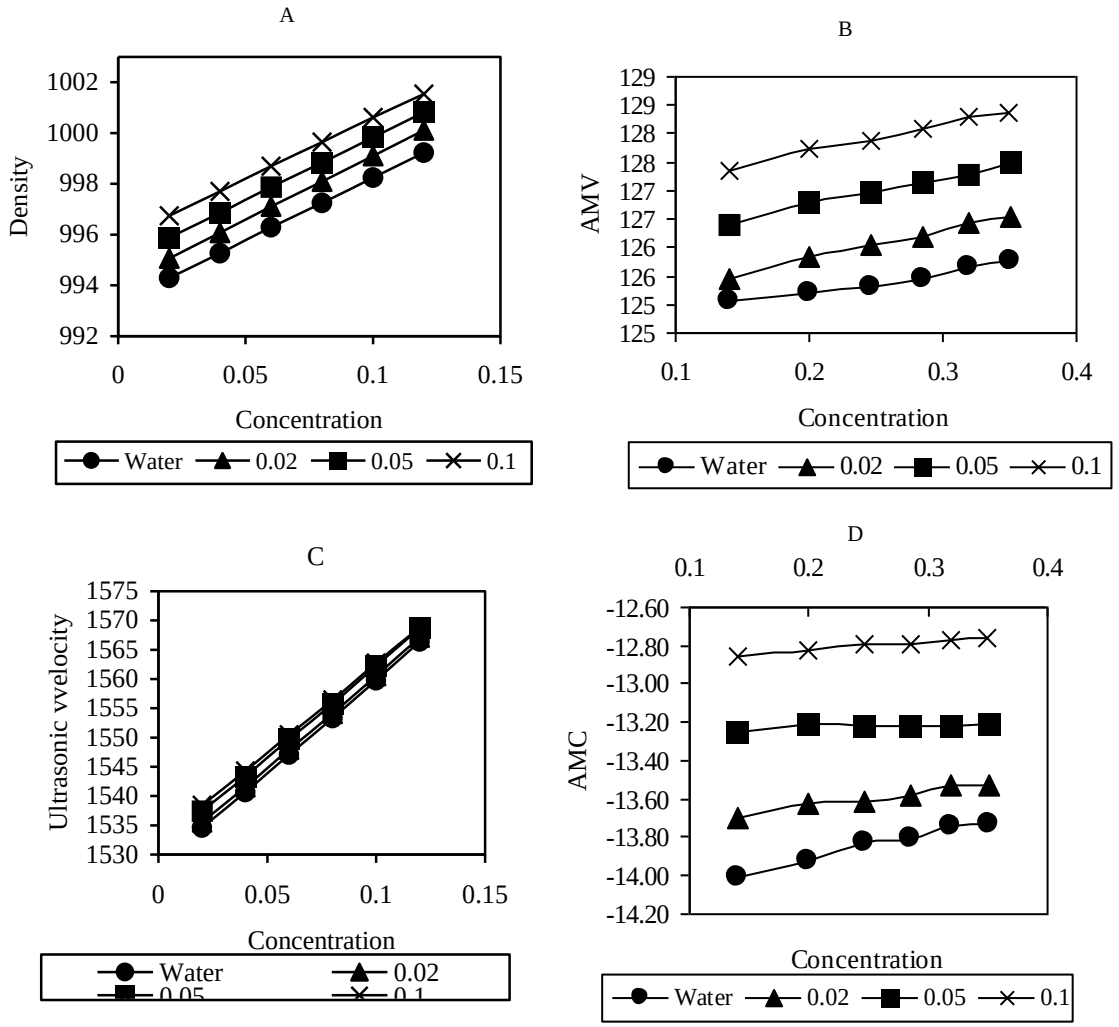
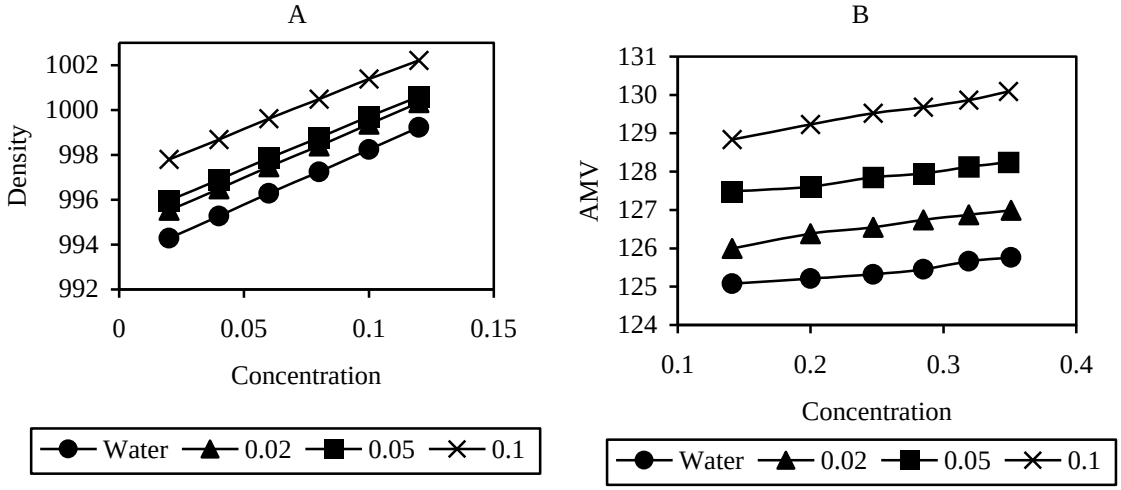


Figure 1 A-D. The, $_{\rho}V_{2,\varphi}$ and $_{u}\Delta\kappa_{2,\varphi}$ values of (Aq. L-Arginine + Glucose) at 310.15 K



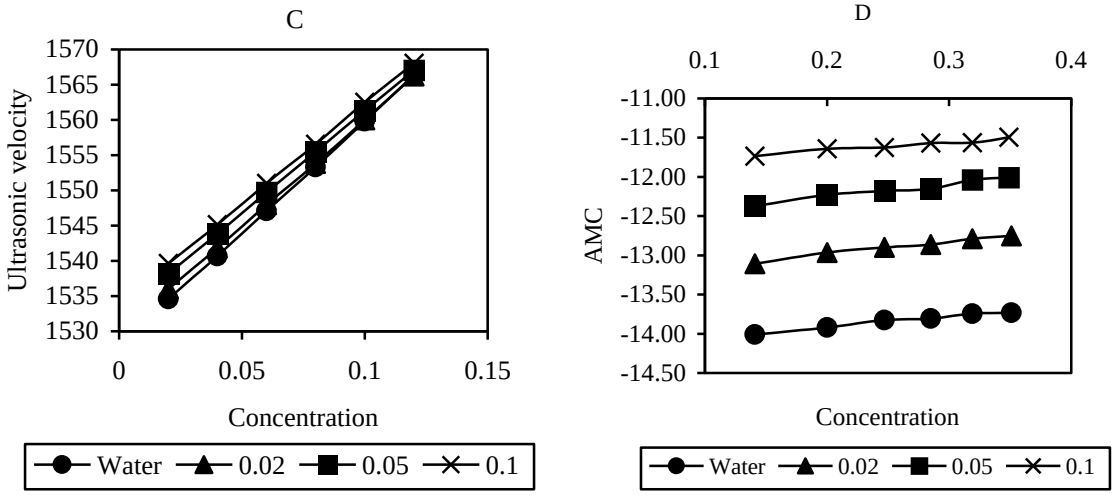


Figure 2 A-D. The, $_{\rho}\ V_{2,\varphi}$ and $_{u}\ \Delta\kappa_{2,\varphi}$ values of (Aq. L-Arginine + Lactose) at 310.15 K

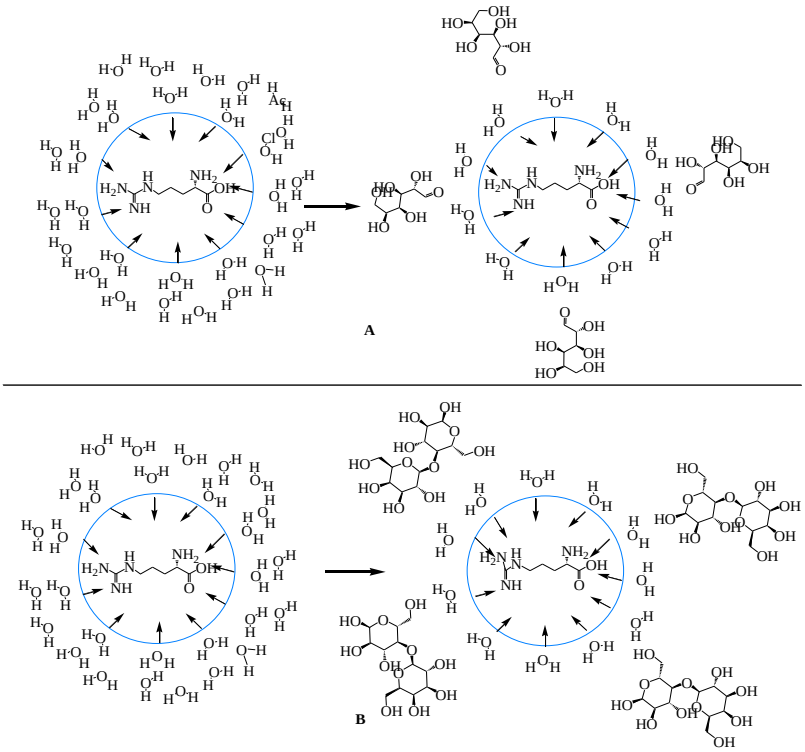
Table 1. The $V^{o}_{2,\phi}$, S_v, $\Delta_t V^{o}_{2,\phi}$ and $\kappa^{o}_{S,2,\phi}$, $\Delta_t \kappa^{o}_{S,2,\phi}$ values of (Aq. L-Arginine + Glucose) at 310.15 K

System/property	$V^{o}_{2,\phi}$	S_v	$\Delta_t V^{o}_{2,\phi}$
Water	124.56	3.307	0.000
0.02M aq. Glucose	124.73	5.267	0.170
0.05M aq. Glucose	125.73	4.954	1.170
0.10 M aq. Glucose	126.69	4.894	2.130
System	$\kappa^{o}_{S,2,\phi}$	S_k	$\Delta_t \kappa^{o}_{S,2,\phi}$
Water	-14.190	1.361	0.000
0.02M aq. Glucose	-13.797	0.781	0.393
0.05M aq. Glucose	-13.256	0.146	0.934
0.10 M aq. Glucose	-12.908	0.426	1.282

Table 2. The $V^{o}_{2,\phi}$, S_v, $\Delta_t V^{o}_{2,\phi}$ and $\kappa^{o}_{S,2,\phi}$, $\Delta_t \kappa^{o}_{S,2,\phi}$ values of (Aq. L-Arginine + Glucose) at 310.15 K

System/property	$V^{o}_{2,\phi}$	S_v	$\Delta_t V^{o}_{2,\phi}$
Water	124.56	3.307	0.000
0.02M aq. Lactose	125.40	4.624	0.840
0.05M aq. Lactose	126.91	3.769	2.350
0.10 M aq. Lactose	128.05	5.801	3.490
	$\kappa^{o}_{S,2,\phi}$	S_k	$\Delta_t \kappa^{o}_{S,2,\phi}$
Water	-14.190	1.361	0.000
0.02M aq. Lactose	-13.318	1.643	0.872
0.05M aq. Lactose	-12.596	1.687	1.594
0.10 M aq. Lactose	-11.873	1.047	2.317

Foot Note: $V^{o}_{2,\phi}$=cm^3·mol^{-1}, S_v=cm^3·mol$^{-3/2}$·kg$^{1/2}$. $\kappa^{0}_{S,2,\phi}$=×10^{-14} m^3·mol^{-1}·Pa^{-1}, S_k=×10^{-14} m^3·**mol$^{-3/2}$**·kg$^{1/2}$ ·Pa^{-1}, $\Delta_t V^{o}_{2,\phi}$=cm^3·mol^{-1}, $\kappa^{0}_{S,2,\phi}$=×10^{-14} m^3·mol^{-1}·Pa^{-1}.



Scheme 1. Hydration of L-Arginine in presence of A) Glucose and B) Lactose

The study has implications in protein-sugar interactions in solution which discloses size of hydration sphere, specific interactions and solution behavior of amino acids in specific and proteins in general. The observations in present systems reveals that the hydrogen bonding and hydrophilic-hydrophilic interactions occurs in L-Arginine and Glucose//Lactose with dominance of these interactions in Lactose solution.

Conclusion:

Hydration structure of L-Arginine affects in presence of cosolutes glucose and Lactose as a result of hydrogen bonding and other interactions in solution. The cosolute causes increase in the volume and compression and weakening of solute-solvent interactions as a cosphere overlap. This effect is dominant in Lactose solutions.

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51

Studies in the Synthesis of 5-(3-Substitutedthiocarbamido) Aminoindole by Microwave Technique

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Abstract: We reported synthesis of 5-(3-thiocarbamido)aminoindol, 5-(3-allylthiocarbamido) aminoindole, 5-(3-*o*-nitrophenylthio- carbamido)aminoindol, 5-(3-*p*-nitrophenylthiocarbamido)aminoindol, 5-(3-*m*-chloro- phenylthiocarbamido)aminoindole by interacting 5-chloroindol with thiourea, allyl thiourea, *o*-nitrophenylthiourea, *m*-chlorophenylthiourea respectively. Ethanol was taken and kept in microwave oven and irradiation was carried out for 2 minutes at 50 °C. The justification and determination of structures of synthesized molecules were done on the basis of elemental analysis, chemical characterizations, IR, H^1-NMR, C^{13}NMR studies.This green synthetic method increases yield of products by maintaining the purity of the products this is the novelty of the research work.

Key words: 5-chloroindole, substituted thiourea, green synthesis, microwave technique.

INTRODUCTION

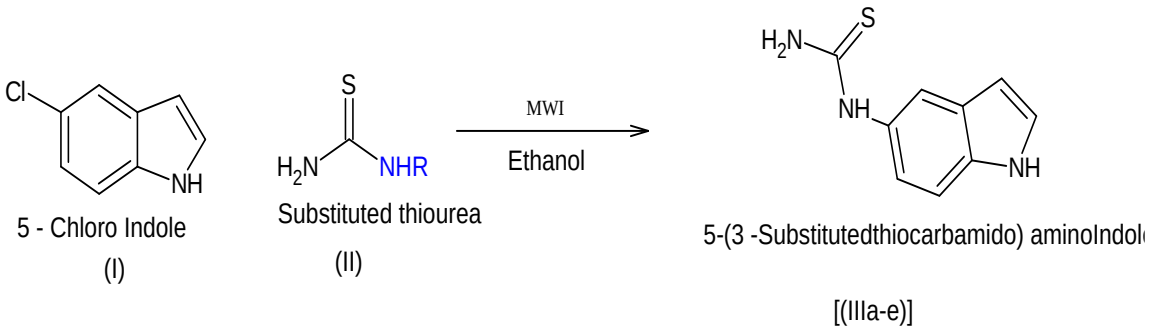
Indole nucleus containing heterocycles created their own identity due to these applications in life, pharmaceutical, medical, and agricultural sciences. Indoles showed anticancer, anti-inflammatory, antioxidant activities[1-3].

Indole based heterocycles are well known recognised for their antimicrobial, anti-micotic and inhibition of chemical mediator's release[4], anti-inflammatory[5-7], anti-asthama[8], anti-vascular[9], antifungal[10], activities.At the same time thiocarbamido nucleus showed antioxidant, anticancer, anti-inflammatory antitubercular activities. Majority of alkaloids contain indole nucleus which exhibits excellent biological activities i.e.antiviral, antitumor, antiplasmodial, antibacterial and neurochemicals melatonin and serotonin are more complex bisindole natural products vincristine and vinblastine these are the key structural component of many effective synthetic pharmaceuticals[4-5].Amino acid tryptophans, the biogenic amines serotonin, tryptamine and the mammalian hormone melatonin are broadly known indole derivatives play an significant role in lively activity of humans and animals[11].

Synthetic applications of cynoguanidine and 1, 3- diformamido-thiocarbamide had been briefly explored[12]. Synthesis of nitrogen, sulphur and nitrogen and sulphur containing heteroacycles and heterocycles the interactions of cynoguanidine with various thiourea and isothiocynates have been investigated in sufficient details [13-18]. Some of these compounds showed remarkable pharmaceutical and biological activities[19-20]. As a wider programme of this research laboratory we have decided to synthesize a novel series of 5-(3-substituted thiocarbamido) aminoindole by interacting 5-chloroindole (I) with thiourea (IIa), allyl thiourea (IIb), *o*-nitro-phenyl thiourea (IIc), *p*-nitro-phenyl thiourea (IId), *m*-chloro-phenyl thiourea(IIe) in presence of ethanol by using microwave technique. Structure determination and

identification of the synthesized product is done on the basis of chemical characteristics, elemental analysis and spectral data.

GENERAL REACTION:-



Where R= -H, -allyl, -*o*-nitrophenyl, -*p*-nitrophenyl, *m*-chlorophenyl

1. EXPERIMENTAL

The melting point of the allsynthesized compounds was recorded using hot paraffin bath. The carbon and hydrogen analysis were carried out on Carlo-Ebra 1106 analyzer. Nitrogen estimation was carried out on Colman-N-analizer-29. IR spectra were recorded on Perkin Elmer Spectrometer in range 4000-400cm^{-1} in KBr pellets. The purity of compound was checked by TLC plate. All chemicals used were of AR-grade.

2.1 5-(3-Thiocarbamido) Amino Indole (IIIa)

A mixture of 5-chloroindole (I) (0.1M, 0.392 gms) and thiourea (0.1M, 0.152 gms) in ethanol was kept in microwave used to synthesis 5-(3-thiocarbamido) amino indole (IIIa) (1 gm, 97.35%), melting point 160^{0}C.(D)

RESULTS AND DISCUSSION

Properties of (IIIa): It is pale yellow colour crystalline solid having melting point 160^{0}c (D). It gave positive test for nitrogen and sulphur. Desulphurised with alkaline plumbite solution. It forms picrate, melting point 120^{0}c. Elemental analysis C {(found 67.58%) calculated 68.30%}, H {(found 5.17%) calculated 5.33%}, N {(found 14.86%) calculated 14.94 %}, S {(found 11.24%) calculated 11.38%}.

IR Spectra

FTIR Spectrum was recorded using KBr-pellets and is reproduced. Important absorption can be correlated as (cm^{-1}): N-H stretching at 3387.00cm^{-1} (3500-3000 cm^{-1}), Ar-H stretching at 2690.70cm^{-1} (3000-2500cm-^{1}), Ar-c=c stretching at 1612.49cm^{-1} (1600-1500cm^{-1}), C-N stretching at 1085.92cm^{-1} (1200-1000cm)$^{-1}$, N-C=S stretching at 1462.04cm^{-1} (1550-1250cm^{-1}), NN>C=S stretching at 1400.89cm^{-1} (1400-1200cm-1).

NMR

This spectrum distinctly displayed signals at (δ ppm): signal at 7.2646-7.1726 ppm is due to Ar-H, signal at 4.2911-4.4564 ppm is due to N-H in aromatic ring, signal at 3.1402-2.2160 ppm is due to NH_2 and -NH protons. ^{13}C Spectrum: This spectrum distinctly displayed signals due to C=S carbon at δ 181.76 ppm, Ar-C carbon at δ 155.58-112.58 ppm, -CH_2 carbons at δ 79.04-78.38 ppm, -CH_3 carbons at δ 4012-38.87 ppm.

2.2 5-(3-Allylthiocarbamido) Amino Indole (IIIb)

A mixture of 5-chloroindole (I) (0.1 M, 1.56 gm) and allyl thiourea (IIb) (0.1 M, 0.68 gm), in ethanolwas kept in microwave used to synthesis 5-(3-allylthiocarbamido) amino indole (IIIb) (2 gm, 90%), melting point 186^0C.(D)

RESULTS AND DISCUSSION

Properties of (IIIb): It is lemon yellow colour crystalline solid having melting point 186^0c (D). It gave positive test for nitrogen and sulfur. Desulphurized with alkaline plumbite solution. It forms picrate, melting point 110^0c. Elemental analysis C {(found 68.58%) calculated 69.27%}, H {(found 5.11%) calculated 5.35%}, N {(found 15.86%) calculated 16.64 %}, S {(found 11.34%) calculated 11.48%}.

IR Spectra

The IR spectra was carried out in KBr pellets and the important absorptions can be correlated as, (cm^{-1}) 3312 (N-H stretching), 1197 (C-N stretching), 3012 (Ar-H stretching), 1736 (N=C-N stretching), 1512 (Ar-C=C), 1487 (N-C=S) Bending.

NMR

Ar-H protons (6.8720-6.8991 ppm), N-H protons (5.0417-5.0471 ppm), N-H of five membered ring (4.2921-4.5564 ppm), -CH3 protons (3.4386-3.8638 ppm).

2.3 5-(3-*o*-nitro-phenyl thiocarbamido) Amino Indole (IIIc)

A mixture of 5-chloroindole (I) (0.1 M, 1.17 gm) and *o*-nitro-phenyl thiourea (IIc) (0.1 M, 1.212 gm), in ethanol was used to synthesis 5-(3-*o*-nitro-phenylthiocarbamido) amino indole (IIIc) (3 gm, 94%), melting point 192^0C.(D)

RESULTS AND DISCUSSION

Properties of (IIIc)-It is orange colour crystalline solid having melting point 192^0c (D). It gave positive test for nitrogen and sulphur. Desulphurisd with alkaline plumbite solution. It forms picrate, melting point 120^0c. Elemental analysis C {(found 63.58%) calculated 64.27%}, H {(found 5.91%) calculated 6.35%}, N {(found 15.06%) calculated 16.64 %}, S {(found 11.34%) calculated 11.48%}.

IR Spectra

The IR spectra was carried out in KBr pellets and the important absorptions can be correlated as, (cm^{-1}) 3312 (N-H stretching), 1197 (C-N stretching), 3012 (Ar-H stretching), 1736 (N=C-N stretching), 1512 (Ar-C=C), 1487 (N-C=S) Bending.

NMR

Ar-H protons (6.8720-6.8291 ppm), N-H protons (5.0417-5.0471 ppm), N-H of five membered ring (4.2920-4.5565 ppm).

2.4 5-(3-*p*-nitro-phenyl thiocarbamido) Amino Indole (IIId)

A mixture of 5-chloroindole (I) (0.1 M, 1.16 gm) and *o*-nitro-phenyl thiourea (IId) (0.1 M, 1.26 gm), in ethanol was used to synthesis 5-(3-*p*-nitro-phenylthiocarbamido) amino indole (IIId) (2.9 gm, 94%), melting point 194^0C.(D)

RESULTS AND DISCUSSION

Properties of (IIId)-It is pale orange colour crystalline solid having melting point 194^0c (D). It gave positive test for nitrogen and sulphur. Desulphurisd with alkaline plumbite solution. It forms picrate, melting point 130^0c. Elemental analysis C {(found 63.98%) calculated 64.57%}, H {(found 4.91%) calculated 5.59%}, N {(found 15.26%) calculated 16.97 %}, S {(found 11.34%) calculated 11.78%}.

IR Spectra

The IR spectra was carried out in KBr pellets and the important absorptions can be correlated as, (cm^{-1}) 3612 (N-H stretching), 1097 (C-N stretching), 3092 (Ar-H stretching), 1796 (N=C-N stretching), 1572 (Ar-C=C), 1447 (N-C=S) Bending.

NMR

Ar-H protons (6.8420-6.8491 ppm), N-H protons (5.0417-5.0471 ppm), N-H of five membered ring (4.2960-4.5566 ppm).

2.5 5-(3-*m*-chloro-phenyl thiocarbamido) Amino Indole (IIIe)

A mixture of 5-chloroindole (I) (0.1 M, 1.36 gm) and *m*-chloro-phenyl thiourea (IIe) (0.1 M, 1.09 gm) in ethanol was used to synthesis 5-(3-*m*-chloro-phenylthiocarbamido) amino indole (IIIe) (2.4 gm, 95%), melting point 193^0C.(D)

RESULTS AND DISCUSSION

Properties of (IIIe)-It is ivory colour crystalline solid having melting point 193^0c (D). It gave positive test for nitrogen and sulphur. Desulphurisd with alkaline plumbite solution. It forms picrate, melting point 180^0c. Elemental analysis C {(found 62.98%) calculated 63.57%}, H {(found 4.31%) calculated 5.89%}, N {(found 14.26%) calculated 15.97 %}, S {(found 11.24%) calculated 11.94%}.

IR Spectra

The IR spectra was carried out in KBr pellets and the important absorptions can be correlated as, (cm^{-1}) 3412 (N-H stretching), 1037 (C-N stretching), 3192 (Ar-H stretching), 1996 (N=C-N stretching), 1672 (Ar-C=C), 1457 (N-C=S) Bending.

NMR

Ar-H protons (6.9420-6.8491 ppm), N-H protons (5.0417-5.0461 ppm), N-H of five membered ring (4.2760-4.5596 ppm).

ACKNOWLEDGMENTS

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52

Understanding the Role of Lipophilicity and Pharmacophore Elements in Pyrimidinedione based BCAT1 Inhibitory Activity

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Abstract:

This paper presents the findings from pharmacophore-oriented studies on BCAT1 inhibitors. Understanding the role of lipophilicity and pharmacophore elements is paramount in elucidating the inhibitory activity of pyrimidinedione-based compounds targeting BCAT1. This study investigated a novel structural class of BCAT1 inhibitors, specifically (trifluoromethyl)pyrimidinediones, identified through high-throughput screening. The research emphasized the significance of lipophilicity, demonstrated by the increased BCAT1 inhibitory action resulting from the substitution of lipophilic groups in the molecular structure. Pharmacophore modeling revealed crucial elements, including hydrogen bond acceptors and donors, influencing the BCAT1 inhibitory activity. The examination of potent inhibitors, such as BAY-069, shaded light on the cellular activity and selectivity of these compounds. The study contributes to a comprehensive understanding of the intricate relationship between lipophilicity, pharmacophore features, and the effectiveness of pyrimidinedione-based BCAT1 inhibitors.

Keywords: Pharmacophore modeling, Pymol, BCAT1 Inhibitors, Pyrimidinedione,

Introduction:

The pursuit of effective cancer treatments has long been at the forefront of medical research, prompting the exploration of innovative therapeutic avenues[1]. Among the promising targets for cancer therapy are the branched-chain amino acid transaminase enzymes (BCAT1 and BCAT2), which play a crucial role in the metabolic reprogramming of cancer cells. These enzymes facilitate the catabolism of branched-chain amino acids (BCAAs), such as leucine, isoleucine, and valine, leading to the generation of key metabolic intermediates necessary for tumor growth and survival[2].

In recent years, significant attention has been directed towards the development of BCAT1/2 inhibitors as potential anticancer agents. Among these, the pyrimidinedione-based inhibitors have emerged as a particularly promising class of compounds with potent inhibitory activity against BCAT1 and BCAT2 enzymes[3].

The overexpression of BCAT1 and BCAT2 has been observed in various cancer types, including breast, prostate, lung, and pancreatic cancers. Their upregulation has been associated with aggressive tumor behavior, metastasis, and resistance to standard cancer therapies. Consequently, targeting these enzymes represents a rational and attractive strategy to disrupt cancer cell metabolism, impair tumor growth, and enhance the efficacy of existing treatments[4].

Pyrimidinedione-based BCAT1/2 inhibitors offer several advantages over traditional anticancer agents. Their unique chemical structure confers a high degree of specificity towards BCAT1 and BCAT2 enzymes, minimizing off-target effects and reducing potential toxicity to normal cells. Moreover, their distinct mode of action disrupts the intricate metabolic networks within cancer cells, creating an environment detrimental to cancer cell survival[5].

Pharmacokinetic profiling plays a pivotal role in drug development, guiding the understanding of how a compound is absorbed, distributed, metabolized, and excreted in the body. This study focuses on the pharmacokinetic profiling of innovative pyrimidinedione-based BCAT1 inhibitors, aiming to unravel essential aspects related to their bioavailability, tissue distribution, and metabolic fate[6]. The investigation explores how these novel compounds interact within the

biological system, with a specific emphasis on their potential implications for optimal drug delivery and therapeutic efficacy. By elucidating the pharmacokinetic behavior of these BCAT1 inhibitors, this research aims to provide valuable insights that can inform the design of effective drug formulations, dosing regimens, and administration routes, ultimately advancing their translational potential in the realm of cancer therapeutics.

Methodology:

1. Selection of Dataset: The consensus pharmacophore model was developed using a dataset of 43 molecules[7]. The molecules were screened for their activity and selectivity for BCAT1 inhibitors. The activity values (IC_{50} expressed as nM) were used to find most active molecules. The Table 1 contains top active molecules and least active molecules which are used for model building.

Table 1. SMILES notations and activity values IC_{50} (nM) of four highly reactive molecules and least active molecule used for alignment

S.N.	SMILES	IC_{50} (nM)
1	Cc1ccccc1Oc2cc(N3C(=O)NC(=CC3=O)C(F)(F)F)c4ccccc4c2Cl	31
2	COc1cc(C#N)c(Oc2ccccc2C)cc1N3C(=O)NC(=CC3=O)S(=O)(=O)c4ccccc4	60
3	COc1cc(C#N)c(Oc2ccccc2C)cc1N3C(=O)NC(=CC3=O)C(F)(F)F	162
4	COc1cc(C#N)c(Oc2ccccc2C)cc1N3C(=O)NC(=CC3=O)C(F)(F)C(F)(F)F	792
5	Cc1ccccc1Oc2ccc(F)c(c2)N3C(=O)NC(=CC3=O)C(F)(F)F	50000

2. Compound Representation, Geometry Optimization & File Format Conversion with Open Babel::

- Chemical structures were drawn using Chem Draw ennsuring accurate depiction of bond types, stereochemistry, and relevant functional groups.
- Optimized the 3D structures of the compounds using Chem Draw or a molecular mechanics tool to refine bond angles and minimize steric clashes
- Identified key pharmacophoric features (e.g., hydrogen bond donors/acceptors, hydrophobic regions) using Chem Draw.
- Annotated each feature with relevant distances and angles.
- Converted the optimized 3D structures to a common format (e.g., MOL) using Open Babel for compatibility with PyMOL.[8]

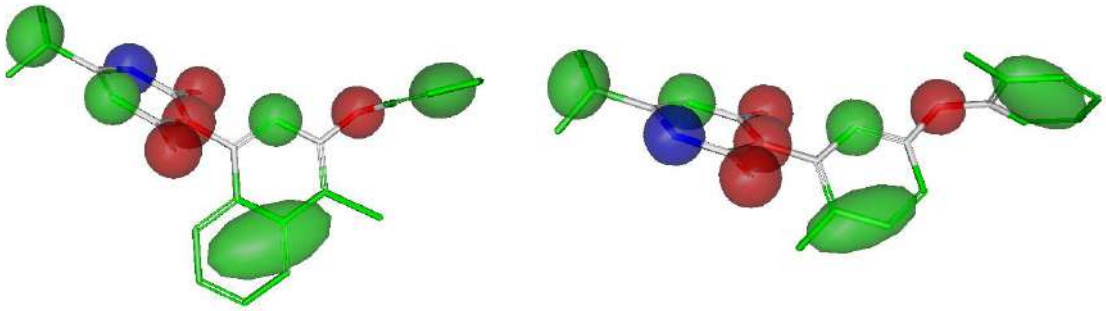
3. Pharmacophore Alignment and Visualization with PyMOL:

- Loaded the converted structures into PyMOL for molecular visualization.
- Aligned the structures based on common pharmacophoric features using PyMOL's alignment tools.
- Visualized and refined the pharmacophore model in PyMOL, considering spatial arrangements.[9]

4. Validation and Refinement & Export Pharmacophore Features:

- Validated the pharmacophore model against known ligand-receptor interactions.
- Refined the model iteratively based on experimental data or additional computational analyses.

- Exported the refined pharmacophore features from PyMOL for further analysis or virtual screening.



(a) (b)

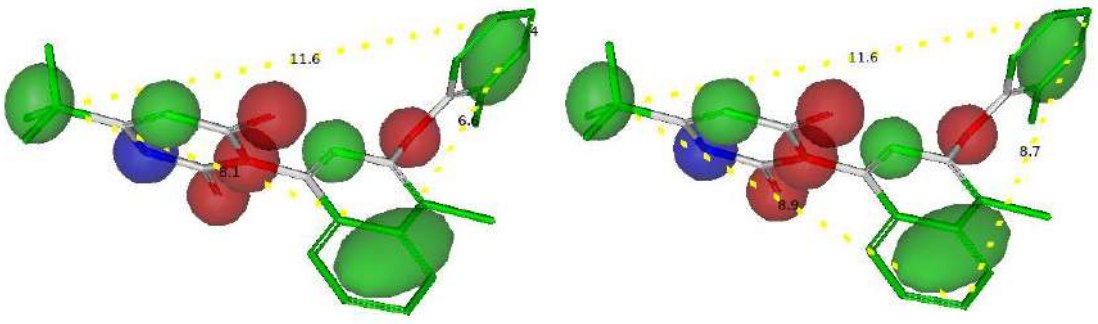
Figure 1. Consensus pharmacophore model (a)Most active Molecule (IC_{50}=31nm) (b) Most active molecule (IC_{50}=5000nm) showing contours for different regions (Green: Lipophilic, Blue: H-Bond donor and Red: H-Bond acceptor region)

Result and Discussions:

The current pharmacophore-oriented research reveals a strong association between the BCAT1 inhibitory activity of the compounds chosen for this investigation and five lipophilic, one H-Bond donor, and four H-bond acceptor groups. However, as the pharmacophore modeling of the other most active compounds listed in the above table shows, the mere presence of a given number of lipophilic, donar, and acceptor regions does not immediately correlate with the level of their activity against BCAT1 enzyme.

Increased lipophilicity of the molecules caused by the substitution of lipophilic groups for the original molecule is thought to be the probable cause of the increased BCAT1 inhibitory action. One nitrogen atom function as a donor and the other two oxygen atoms on the pyrimidinedione ring as H-bond acceptors. According to published research, these medicinal compounds' ability to bind BCAT1 inhibitors is directly impacted by regions that are more lipophilic.

Figure 1 examination demonstrates that the lipophilic character of the bicyclic and aromatic rings of pyrimidinedione-based BCAT1 inhibitors is responsible for the BCAT1 inhibitory activity of BAY-069 derivatives.



(a-1) (a-2)

Figure 2: Intramolecular distances (pm) of lipophilic region

Based on pharmacophore-oriented study, the selected compounds have five lipophilic, one H-bond donor, and four H-bond acceptor groups, all of which are positively correlated with BCAT1 inhibitory action. Yet, as previous highly active molecules have demonstrated, the

fixed number of these regions alone does not directly correlate with the strength of BCAT1 inhibitory activity[10].

Increased lipophilicity brought about by molecule replacement with lipophilic groups is thought to be the cause of the increased BCAT1 inhibitory action. Increased lipophilic surfaces affect the intramolecular distances of lipophilic regions, H-bond donors, and H-bond acceptors, which in turn affects how certain BCAT1 amino acids interact (Figure 2).

Conclusions: The pharmacophore-oriented exploration of BCAT1 inhibitory activity reveals a nuanced connection between molecular characteristics and compound efficacy. While the presence of lipophilic, donor, and acceptor groups correlates positively with BCAT1 inhibition, this relationship is not solely dictated by their fixed quantity. Pharmacophore modeling of highly active compounds underscores the influence of additional factors on overall BCAT1 enzyme activity. Enhanced lipophilicity, achieved through substituting lipophilic groups, significantly contributes to heightened BCAT1 inhibitory effects. This involves the introduction of lipophilic moieties, increasing relevant surfaces, impacting intramolecular distances, and influencing interactions with BCAT1 amino acids. The nitrogen and oxygen atoms on the pyrimidinedione ring, serving as H-bond donor and acceptors, respectively, emphasize the crucial role of these structural elements. In conclusion, this research underscores the intricate interplay of molecular features in BCAT1 inhibitory activity, stressing the need for a comprehensive understanding beyond the mere presence of specific pharmacophoric elements. Future BCAT1-targeted drug design should consider quantitative aspects, spatial arrangements, and interactions for potent inhibitor development.

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53

Use of Formic Acid as Co Surrogates in Palladium Catalyzed Carbonylation Reaction

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ABSTRACT:

Carbonylation is the process of utilizing carbon monoxide (CO) as a highly effective building block in organic transformations. Nevertheless, managing this hazardous and environmentally impactful CO gas poses a significant challenge for chemists. To address this concern, toxic carbon monoxide gas has been substituted with alternative CO sources referred to as CO surrogates. Formic acid and formaldehyde have proven to be highly applicable in organic synthesis and are consequently utilized as non-gaseous CO surrogates. This article outlines recent advancements in the exploration of formic acid as a CO surrogate in transition-metal catalyzed carbonylation reactions.

Keywords: Carboxyboronate, Carbon building block, C-C coupling, Carbonylation

INTRODUCTION:

Transition-metal-catalyzed carbonylations represents an important class of reactions for the effective preparation of range of carbonyl-containing compounds (Cornils 2009). The Carbonylation reaction allows one step insertion of CO to a substrate therefore much efforts has been made to explore the new carbonylative transformations (Wang 2010). The first carbonylation reaction catalyzed by transition metal using gaseous carbon monoxide (CO) was demonstrated Heck and co-workers in 1974 (Schoenberg 1974). This discovery set milestone in use of gas phase reaction.

There is a major drawback with a carbonylation reaction is that in most cases, the highly toxic, tasteless, odorless, and colorless gas carbon monoxide is required, and it is often exploited in large excess and in many instances at higher pressure then the atmospheric (Cao, 2017). The laboratories also need special CO detectors and possibly high pressure reactors limit the use of this CO gas (Khedkar, 2011). As a result of the physical properties of carbon monoxide, its use in the fine chemical industry and academia is limited. Thus in context of solving this problem, carbonylations without the use of CO gas become better alternative for synthetic organic chemists.

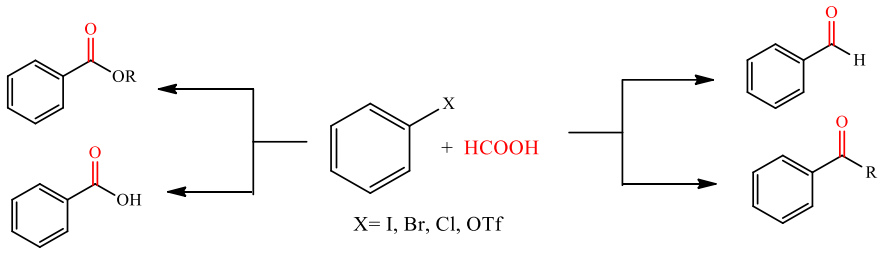
In this respect, in 2004 Morimoto and Kakiuchi explored the CO surrogates for Pauson–Khand reactions, carbonylation reactions by using aromatic halides, and sometime applied for alkenes.(Morimoto, 2004) Since then, many research projects have addressed new strategies and new carbonyl sources. (Park, 2010)

M. Larhed and co-workers reviewed the molybdenum hexacarbonyl as a solid surrogate for the carbonylative insertion reactions (Odell, 2012). Beller et al. summarized different carbonylation reactions using alkenes as a substrate with CO surrogates (Wu, 2014). Use of formic acid derivatives like phenyl formate and N-formylsaccharin as CO surrogates was demonstrated by Konishi and Manabe (Konishi 2014). Bhanage and co-workers focused on alkynes, arenes and aryl halides as a substrate for carbonylation reaction catalyzed by

transition-metal using CO surrogates (Gautam, 2015). Use of COgen (9-methylfluorene-9-carbonyl chloride) and SilaCOgen (methyldiphenylsilacarboxylic acid) was explored by Skrydstrup and co-workers (Friis, 2016). Unlike these CO surrogates, formic acid and there salt also found to be an excellent source of CO. However, formic acid (HCOOH) was successful applied carbonylation reactions. Hence present article address the recent updates in use formic acid and there salt in CO free carbonylation reactions.

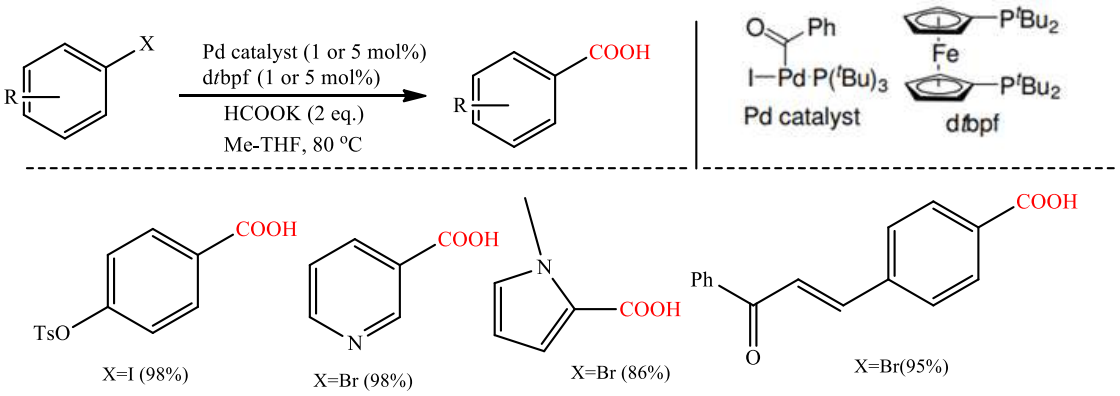
Use of Formic Acid in Palladium-Catalyzed Carbonylation reactions

Thus in search of new safer CO surrogates, for the first time Simonato discovered use of formic acid as a CO source (Simonato, 2003). After this discovery first palladium catalysed Carbonylation reaction using formic acid as alternative to CO was explored by Cacchi and co-workers (Scheme 1) (Cacchi, 2003). They studied the hydroarylation reactions of alkynes with aryl halides catalyzed by palladium by employing formate anions as reducing agents. They found that in the presence of acetic anhydride, formate anion can act as CO surrogate. They also projected a mechanism which comprising the formation of formic acetic anhydride from formate anion and acetic anhydride. The reaction proceed with the thermal decomposition to generate acetic acid and carbon monoxide, which underwent in-situ palladium-catalyzed hydroxycarbonylation.



Scheme 1:- Palladium catalyzed carbonylation reaction using formic acid as a CO source.

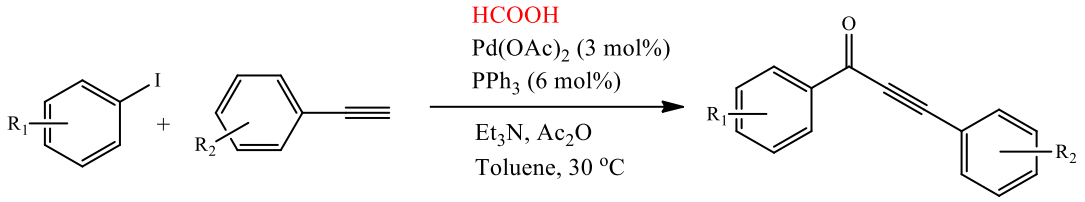
Bessmernykh and Caille et al explored the combination of palladium(II) acetate with 1,1'-bis(diphenylphosphino)ferrocene(dppf) as a catalytic combination for hydroxycarbonylation of aryl and vinyl bromides (Scheme 2) (Berger, 2006).



Scheme 2:- Palladium catalyzed hydroxycarbonylation using formic acid as a CO source.

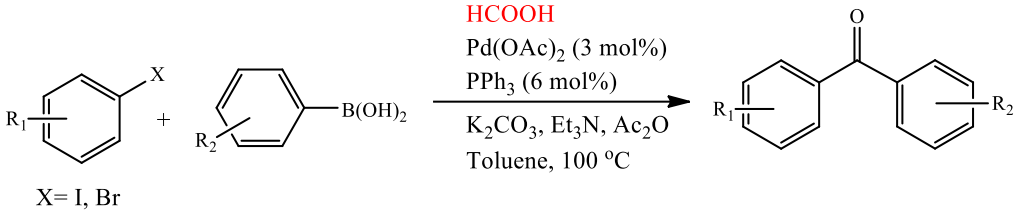
Skrydstrup and co-workers discovered use potassium salt of formic acid (HCOOK) as CO source for carbonylation reaction (Korsager, 2013). An acyl Pd(II) complex was employed as a pre-catalyst with dtbpf as ligand. The reaction condition was tested for different substates.

The cross-coupling reaction involving CO is a powerful carbon-carbon bond formation process which leads to synthesis of range of useful carbonyl compounds like ketones, Amides or esters etc. Carbonylative Coupling of alkyne with aryl iodide i.e Sonogashira coupling using formic acid as carbon monoxide surrogates has been reported by Wu and co-workers (Scheme 3). (Qi, 2015)



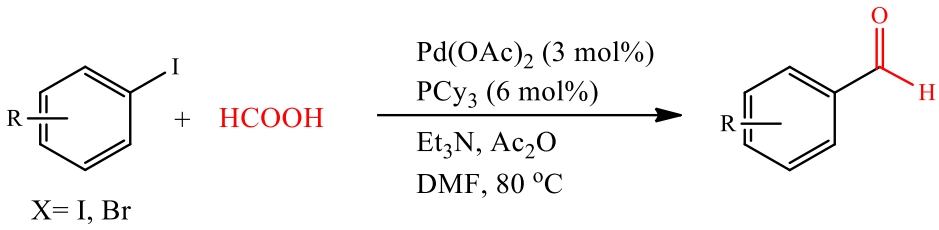
Scheme 3:- Palladium catalyzed Sonogashira coupling employing formic acid as CO surrogates.

Carbonylative Suzuki coupling employing reaction of aryl halides and arylboronic acids in occurrence of formic acid was published by Qi et al. (Scheme 4). (Qi, 2015) Same group further reported synthesis of ester using Palladium catalysed Alkoxycarbonylation under Formic acid (Qi, 2016)



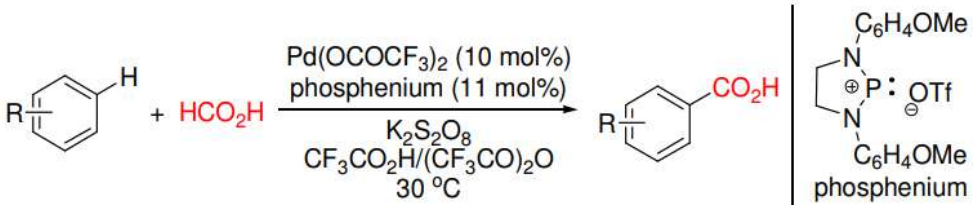
Scheme 4:- Palladium catalyzed Suzuki coupling with formic acid as CO surrogates.

Wu and co-workers explored Palladium-catalyzed reductive carbonylation of aryl iodides with formic acid as the formyl source. This protocol gave direct access to wide range of Aromatic aldehyde in single step (Scheme 5). (Wu 2016)



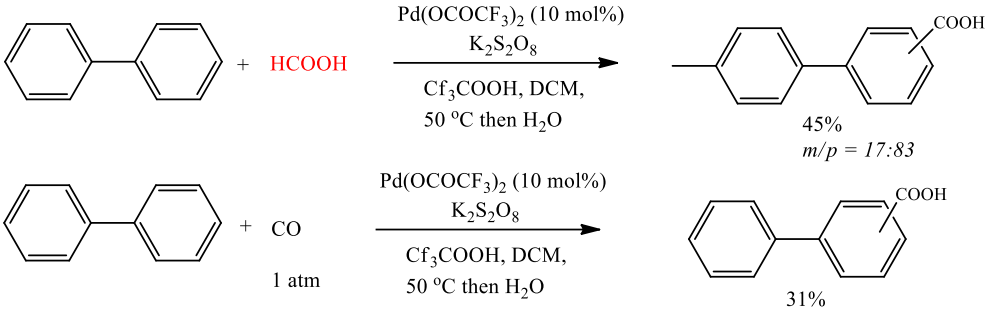
Scheme 5:- Reductive carbonylation of aryl iodides with formic acid by sing Palladium

Nozaki and co-workers developed Palladium-catalyzed hydroxycarbonylation of arenes via aromatic C–H bond activation using formic acid as a source of carbonyl (Shibahara, 2004). During this Surprisingly, they found that, simultaneously hydroxylation and carboxylation of biphenyl to give 4'-hydroxy-4-biphenylcarboxylic acid in the presence of formic acid, whereas with carbon monoxide gas instead of formic acid, the reaction only give hydroxycarbonylation product (Scheme 6).



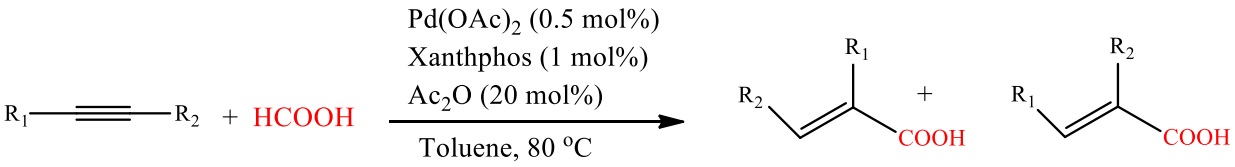
Scheme 6:- Hydroxycarbonylation of arenes via aromatic C-H bond activation using formic acid.

Shi and group developed hydrocarboxylation of olefins with HCOOH and HCOOPh catalyzed by palladium. In this reaction HCOOPh was used in catalytic amount. Using same reaction condition lactones and β-amino acid derivatives were also prepared (Scheme 7) (Wang, 2014)



Scheme 7:- Hydroxycarbonylation of arenes via aromatic C-H bond activation using formic acid.

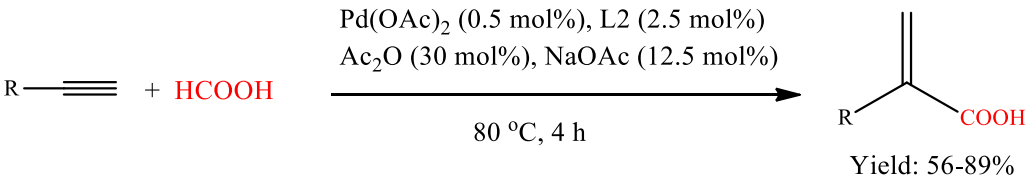
In 2015, Zhou and co-workers proposed hydrocarboxylation of alkynes and formic acid catalyzed by palladium and xantphos. The reaction circumvents a novel method for the synthesis of acrylic acids under mild carbonylation deprived of external CO gas. A catalytic amount of acetic anhydride was utilized for release of carbon monoxide (Scheme 8) (Hou, 2015).



Scheme 8:- Hydrocarboxylation reaction of alkynes and formic acid with Palladium Xantphos.

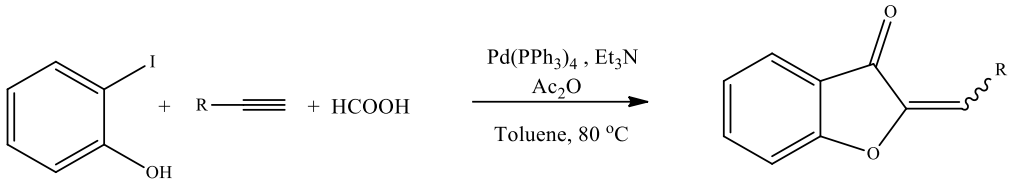
Fu et al. further promoted Nickel catalysed hydrocarboxylation of various alkynes with HCOOH, in which 1,2-bis(diphenylphosphino)-benzene (dppbz) or *cis*-1,2 bis(diphenylphosphino)ethylene (dppen) was used as ligand (Scheme 14) (Fu, 2016)

In 2018 selective palladium-catalyzed alkoxycarbonylation of all kinds of alkenes with formic acid (HCOOH, FA) was described Sang et al (Sang. 2018). Different alkenes including terminal, di-, tri-, and tetra-substituted olefins were transformed into linear esters with very good yields and regioselectivity. Very recently hydrocarboxylation of terminal alkynes with formic acid was reported by Liu and group (Liu, 2022) different α,β-unsaturated carboxylic acids with excellent branched regioselectivity were prepared in one step (Scheme 9).



Scheme 9:- Terminal alkynes with formic acid for Hydrocarboxylation raction

Xinxin Qi et al. first reported the synthesis of aurone using Formic acid as a CO source.[Qi, 2016] In this strategy, in situ CO was generated using formic acid and acetic anhydride which then employed in carbonylation of 2-iodophenol with terminal alkynes. They also screen different Pd catalyst, solvents, and bases for optimization (Scheme 10).



Scheme 10:- Synthesis of aurone using Formic acid as a CO source.

CONCLUSION

This review highlights the recent advancements in carbonylation reactions, with a particular focus on formic acid as a substitute for CO. The shift from toxic CO gas to a cost-effective, readily accessible, and convenient CO source such as formic acid has garnered considerable attention in recent times. The literature reveals diverse approaches, including cross-coupling reactions of organic halides, hydroxycarbonylation, reductive carbonylation, and carbonyl insertion into C-H bonds, showcasing the versatility and widespread application of formic acid in these processes.

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54

In-Silico Prediction of Phytoconstituents From *Solanum Indicum* for Antianxiety Activity

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ABSTRACT

Objective Anxiety is a common reaction to stress, and it may even be beneficial in certain situations. It can alert us to potential dangers and help with planning and focus. Instead of the usual sensations of apprehension or anxiety, there is excessive fear or anxiety when anxiety disorders are present. Compounds found in medicinal plants have been the source of many conventional medications. *In-silico* testing of *Solaum indicum* phytoconstituents for antianxiety efficacy was a part of our investigation.

Methods Utilizing Discovery studio, molecular docking is done to assess the pattern of interaction between the phytoconstituents from the *Solanum indicum* plant and the crystal structure of the stress proteins (PDB ID: 5XVG). Later, SwissADME and pkCSM were used to screen for toxicity as well as the pharmacokinetic profile.

Results The docked results suggest that Solafuranone (-8.1 kcal/mol) and Isofraxidin (-6.8 kcal/mol) for 5XVG macromolecule has best binding towards antianxiety activity as compared to the standard (Gabapentin) for 5XVG is -5.1 kcal/mol. Furthermore, pharmacokinetics and toxicity parameters were within acceptable limits according to ADMET studies.

Conclusion

Results from the binding potential of phytoconstituents aimed at antianxiety activity were encouraging. It promotes the usage of *Solanum indicum* and offers crucial details on pharmaceutical research and clinical care.

1. INTRODUCTION

In traditional Chinese medicine, the plant *Solanum indicum* is used to treat wounds and reduce inflammation because it contains special dioscins, or indiosides. Our earlier research showed that a number of synthetic indiosides derived from Solanum indicum has strong anticancer properties, whereas other compounds have CNS depressing properties.[1]

Solanum indicum is a plant that is eaten as a vegetable in some parts of Africa, and folk medicine experts claim that it may fend off cardiovascular conditions. The research on how it can be utilised to treat hypertension was fascinating. The presence of chlorogenic acids may only have served as a supportive role in the extract's strong therapeutic and preventive effects against hypertension. Other ingredients could be responsible for the antihypertensive impact. Future investigation into the extract as a potential therapy for hypertension is encouraged by the results.[2]

However, there are few studies on the phytoconstituents of *Solanum indicum* for the antianxiety activity. Thus, keeping the above information in view, the present investigation was designed to identify the potential phytochemicals of *Solanum indicum* against 5XVG using a molecular docking method.

2. MATERIALS AND METHODS

2.1. Platform for molecular docking

The computational docking study of all the phytoconstituents selected as ligands with antianxiety activity as the target was performed using PyRx software.[3]

2.2. Protein preparation

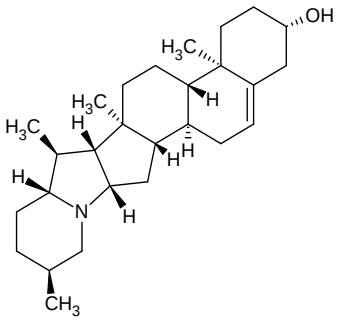
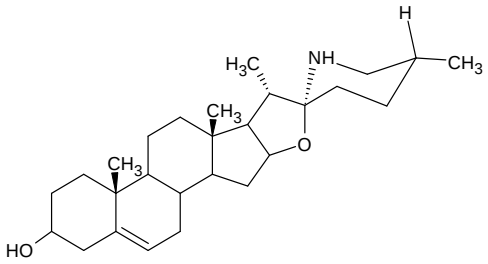
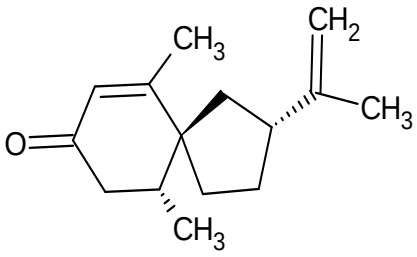
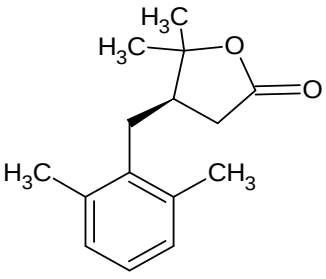
The macromolecule is 5XVG, *in silico* analysis of selected phytoconstituents was performed on the 2.15 Å crystal structure of antianxiety macromolecule with inhibitor, (PDB ID: 5XVG, having resolution Resolution: 2.10 Å, R-Value Free: 0.235, R-Value Work: 0.181, R-Value Observed: 0.184), which was retrieved from the protein data bank (https://www.rcsb.org). 5XVG is classified as crystal structure of PAK4 in complex with the inhibitor CZH226 all other molecules, such as co-crystallized water molecules, unwanted chains, and nonstandard residues, were deleted. Using Discovery studio.[4]

2.3. Mechanism of Action

5XVG: DI-1859 is a potent, selective and covalent DCN1 inhibitors. Mass spectrometric analysis and co-crystal structures reveal that this compound employ a unique mechanism of covalent bond formation with DCN1. The p21-activated kinases (PAKs) are serine/threonine (Ser/Thr) protein kinases that have been identified as downstream signaling effectors of Rho-family GTPases. PAK4 is the most studied group II PAK member, and it has a place at critical nodal points in multiple signaling pathways that are associated with cell growth, cytoskeletal dynamics, cell polarity, survival, and development. PAK4 is particularly highly expressed in prostate, testis, lung, heart, brain, and liver.[5]

2.4. Ligand preparation

The three-dimensional (3D) structures of all constituents were retrieved using Avogadro software from the PubChem database available on the NCBI website (https://pubchem.ncbi.nlm.nih.gov/). However, the drawing of geometrical 2D structure was performed using the ChemSketch program. The two-dimensional (2D) structures were transformed into 3D models using the Avogadro software and the ligand structures were saved in the PDB format. All the chemical structures are shown in Figure 1.

Solanidine 	Solasodine 
Solavetivone 	Solafuranone 

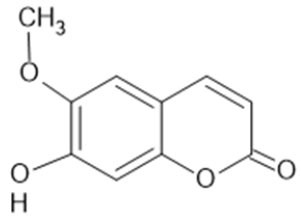
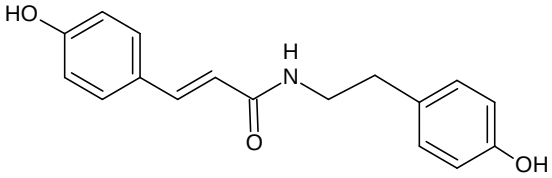
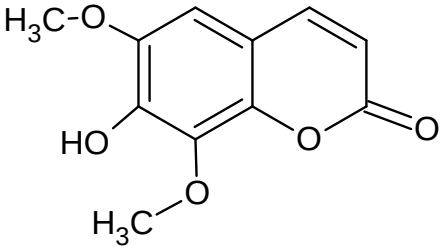
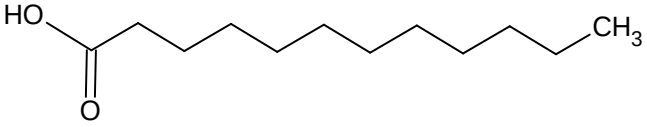
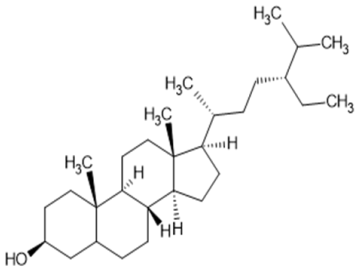
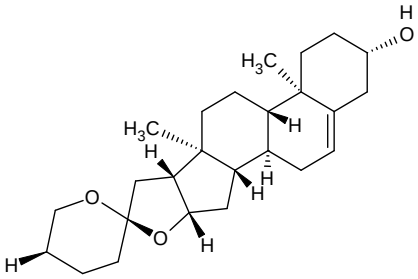
Scopoletin 	N-p-trans-Coumaroyltyramine 
Isofraxidin 	Lauric acid 
β-sitosterol 	Diosgenin 

Fig. 1. Chemical structures of all selected phytoconstituents in the molecular docking studies

2.5. Standard Preparation

The standard is prepared steps such as, the 2D structure of standard drug was made using chem sketch program, then the 2D structure was converted into 3D model using Avogadro Software, it was saved in PDB format.

By using PyRx molecular docking of Gabapentin was done with 5XVG.

2.6. Molecular docking

Molecular docking evaluates the protein-ligand interactions and estimates the scoring function based on the geometry to predict the binding affinity of the ligand molecule[6,7]. We applied molecular docking studies to investigate the binding pattern of selected phytoconstituents (Figure 1) and the standard drug, along with the crystal structure of antianxiety activity macromolecule (PDB ID: 5XVG). The molecular docking study was performed using PyRx software, Binding affinity was explored using the Vina wizard tool. The final results were analysed and visualized using Discovery Studio 2020 Client [8], with bound ligands as the standard. Visualization of protein ligand interaction reflects the number of interactions and active residues responsible for significant binding at the active site of the target enzyme.

2.7. Absorption, distribution, metabolism, and excretion (ADME) and toxicity prediction

The selected phytoconstituents and standard drug were further checked for drug-likeness properties according to Lipinski's rule. During drug development, it is necessary to predict the tolerability of phytochemicals before being ingested by humans and animal models. The pharmacokinetic profile (ADME) and toxicity predictions of ligands were conducted using SwissADME (http://www.swissadme.ch) and pkCSM (an online server database predicting small-molecule pharmacokinetic properties using graph-based signatures, (http://biosig.unimelb.edu.au/pkcsm/prediction). To analyse the toxicological properties of ligands, Simplified Molecular Input Line Entry System (SMILES) notations or PDB files were uploaded, followed by selecting the required models for generating numerous information about structure-related effects[9,10].

3. RESULT AND DISCUSSION

The present study aimed to explore the inhibitory potential of the phytoconstituents present in *Solanum indicum* targeting antianxiety activity. In this study, we performed molecular docking studies of all phytoconstituents found in *Solanum indicum* using AutoDock Vina, followed by a study of interacting amino acid residues and their influence on the inhibitory potentials of the active constituents. Selected phytoconstituents showing the best fit were further evaluated for absorption, distribution, metabolism, excretion, and toxicological (ADMET) properties using SwissADME and pkCSM servers.

3.1 Molecular docking

The docking scores and binding energies of all chemical constituents of *Solanum indicum* targeting antianxiety activity (PDB ID: 5XVG) and binding interactions with amino acid residues are presented in Table 1 respectively.

Table 1. Binding interaction of ligands from *Solanum indicum* targeting antianxiety activity (PDB ID:5XVG)

Sr. No.	Chemical constituent	PubChem ID	Docking Score
			5XVG
1.	Solanidine	65727	-8.0
2.	Solasodine	5250	-8.3
3.	Solavetivone	442399	-6.3
4.	Solafuranone	11107208	-8.1
5.	Scopoletin	5280460	-6.7
6.	N-p-trans-Coumaroyltyramine	5372945	-6.7
7.	Isofraxidin	5318565	-6.8
8.	Lauric acid	3893	-4.2
9.	β-sitosterol	222284	-7.4
10.	Diosgenin	99474	-8.0
Standard Drug			
11	Gabapentin	3446	-5.1

The binding affinities of phytoconstituents ranged from –8.3 to −4.2 kcal/mol. From the docked results, it is evident that the compounds, Solasodine exhibit the most favourable binding affinity (−8.3 kcal/mol) in complex with selected macromolecules (PDB ID: 5XVG) as compared to other docked compounds i.e., Solafuranone (−8.1 kcal/mol), Solanidine (-8.0 kcal/mol), Diosgenin (-8.0 kcal/mol), , Beta sitosterol (-7.4 kcal/mol), Isofraxidin (−6.8 kcal/mol), Scopoletin (−6.7 kcal/mol), N-p-trans-Coumaroyltyramine (−6.7 kcal/mol), Solavetivone (−6.3 kcal/mol), Lauric acid (−4.2 kcal/mol). Visual examination of the

computationally docked optimal binding poses of phytoconstituents on selected macromolecules (i.e., 5XVG) revealed the significant involvement of various types of interactions, such as hydrogen bonding and hydrophobic interactions, including π–π stacking and π–alkyl and alkyl interactions, in the stability of the binding of the phytoconstituents to 5XVG.

The binding affinity of the standard (Gabapentin) for 5XVG is -5.1 kcal/mol.

3.1.1. Solafuranone, 5XVG

An analysis of the interactions between the 5XVG protein complex and the Solafuranone ligand was also carried out, which showed that the ligand molecule is oriented due to Pi-Sigma interaction with LEU A:447 amino acid residue and Pi-Alkyl interaction with ALA A:348, VAL A:335 amino acid residue were found.

3.1.2. Isofraxidin, 5XVG

An analysis of the interactions between the 5XVG protein complex and the Isofraxidin ligand was also carried out, which showed that the ligand molecule is oriented due to Pi-Sigma interaction with VAL A: 335, LEU A: 447 amino acid residue and Alkyl and Pi-Alkyl interaction with ALA A: 348, MET A: 395, LYS A: 350 amino acid residue Conventional Hydrogen bond with LEU A: 398, ASP A: 458 amino acid residue and Carbon hydrogen bond with GLU A: 329 amino acid residue were found.

3.1.3. Gabapentin, 5XVG

The binding affinity of the standard (Gabapentin) for 5XVG is -5.1 kcal/mol. the interactions between the 5XVG protein complex and the Gabapentin ligand was also carried out, which showed that the ligand molecule is oriented due to conventional hydrogen bond with the ASP A:444, SER A:443, GLU A:507 amino acid residue and attractive charge interaction with LYS A:442 amino acid residue were found.

Table No. 2. Interactions with Amino acid residue

Sr. No.	Molecule	Binding Energy (kcal/mol)	H bond	Main amino acid interactions	
				Pi-alkyl, alkyl, Pi-S/Pi-Pi, T shaped/halogen/unfavourable donor-donor interactions	Van der Waals interactions
1	Solanidine	-8.0	GLY A: 452	PRO A: 578, ALA A:423, ALA A: 419	No interactions
2	Solasodine	-8.3	No interactions	PRO A: 479, TYR A: 480, PHE A: 516	No interactions
3	Solavetivone	-6.3	VAL A: 454, ASN A: 377	PRP A: 578, LEU A: 422	No interactions
4	Solafuranone	-8.1	No interactions	VAL A: 335, ALA A: 348, LEU A: 447	No interactions
5	Scopoletin	-6.7	LEU A: 398	MET A:395, ALA A: 402, VAL A: 335, ALA A: 348, LEU A: 447	No interactions

6	N-p-trans-Coumaroyltyramine	-6.7	GLU A: 329, ASP A:440	ASP A: 458, SER A: 331, ILE A: 327	No interactions
7	Isofraxidin	-6.8	LEU A: 398, ASP A: 458, GLU A: 329	LEU A: 447, ALA A: 348, VAL A: 335, MET A: 395, LYS A:350	No interactions
8	Lauric acid	-4.2	PHE A: 304, SER A: 300	ILE A: 369, VAL A: 368, PHE A: 364	ARG A: 360
9	β-sitosterol	-7.4	No interactions	VAL A: 335, LEU A: 447, ALA A: 348, ILE A: 327, ILE A: 337	No interactions
10	Diosgenin	-8.0	No interactions	PRO A: 578	No interactions
11	Gabapentin	-5.1	ASP A: 444, SER A: 443, GLU A: 507	TRP A: 481	LYS A: 442

3.2. ADMET study

Pharmacokinetic profile (ADME) and toxicity predictions of the ligands are important attentive parameters during the transformation of a molecule into a potent drug. In the present study, these parameters were assessed using SwissADME and pkCSM. The absorption potential and lipophilicity are characterized by the partition coefficient (Log *P*) and topological polar surface area (TPSA), respectively. For better penetration of a drug molecule into a cell membrane, the TPSA should be less than 140 Å. However, the value of Log *P* differs based on the drug target. The ideal Log *P* value for various drugs are as follows: oral and intestinal absorption, 1.35 − 1.80; sublingual absorption, > 5; and central nervous system (CNS)[11]. The aqueous solubility of ligands ideally ranges from − 6.5 to 0.5 [12], while the blood brain barrier (BBB) value ranges between − 3.0 and 1.2 [13]. In addition, non-substrate P-glycoprotein causes drug resistance [14].
In our study, all the selected ligands followed the TPSA parameter, P-glycoprotein non-inhibition, thereby showing good intestinal absorption and an acceptable range of BBB values. All the compounds showed aqueous solubility values within the range. Further, it was predicted that the selected ligands do not show AMES toxicity, hepatotoxicity, and skin sensitivity. In addition, it did not inhibit hERG-I (low risk of cardiac toxicity). Lipinski's rule violations, *T. pyriformis* toxicity, minnow toxicity, maximum tolerated dose, rat acute oral toxicity, and chronic toxicity are depicted in table.

Table 3. ADME and toxicity predicted profile of ligands with superior docking score

ADMET Properties	Formula	MW (g/mol)	Log P	TPSA (Å^2)	HB donor	Hb acceptor	Aqueous solubility (Log mol/L)	Human intestinal absorption (%)	Blood Brain Barrier
Solanidine	$C_{27}H_{43}NO$	397.647	5.655	23.47 Å^2	1	2	-4.927	92.975	0.695

Solasodine	$C_7H_{43}NO_2$	413.64	5.2869	41.49 Å^2	2	3	-3.809	92.324	0.035
Solavetivone	$C_{15}H_{22}O$	218.33	3.9042	17.07 Å^2	0	1	-4.615	95.873	0.635
Solafuranone	$C_{15}H_{20}O_2$	232.323	3.18764	26.30 Å^2	0	2	-3.551	95.523	0.206
Scopoletin	$C_{10}H_8O_4$	192.17	1.5072	59.67 Å^2	1	4	-2.504	95.277	-0.299
N-p-trans-Coumaroyltyramine	$C_{17}H_{17}NO_3$	283.327	2.4699	69.56 Å^2	3	3	-3.165	90.031	-0.552
Isofraxidin	$C_{11}H_{10}O_5$	222.196	1.5158	68.90 Å^2	1	5	-2.458	95.588	-0.377
Lauric acid	$C_{12}H_{24}O_2$	200.322	3.9919	37.30 Å^2	1	1	-4.181	93.379	0.057
β-sitosterol	$C_{29}H_{50}O$	414.718	8.0248	20.23 Å^2	1	1	-6.773	94.464	0.781
Diosgenin	$C_{27}H_{42}O_3$	414.63	5.7139	38.69 Å^2	1	3	-5.713	96.565	0.2
Gabapentin	$C_9H_{17}NO_2$	171.24	1.3703	63.32 Å^2	2	2	-2.778	93.257	-0.178

Table 3 Continued

ADMET Properties	P-glyco-protein substrate	Total clearance [Log mL/(min.kg)]	Bioavailability score score	AMES toxicity	Max tolerated dose [Log mg/(kg.d)]	hERG I inhibitor	hERG II inhibitor
Solanidine	YES	0.028	0.55	NO	-0.882	NO	YES
Solasodine	YES	0.09	0.55	NO	-0.375	NO	YES
Solavetivone	NO	1.225	0.55	NO	0.044	NO	NO
Solafuranone	NO	1.256	0.55	NO	0.526	NO	NO
Scopoletin	NO	0.73	0.55	NO	0.614	NO	NO
N-p-trans-Coumaroyltyramine	YES	0.265	0.55	NO	-0.213	NO	YES
Isofraxidin	NO	0.713	0.55	NO	0.56	NO	NO
Lauric acid	NO	1.623	0.85	NO	-0.34	NO	NO
β-sitosterol	NO	0.628	0.55	NO	-0.621	NO	YES
Diosgenin	NO	0.328	0.55	NO	-0.559	NO	YES
Gabapentin	NO	0.525	0.55	NO	0.789	NO	NO

Table 3 Continued

ADMET Properties	Acute oral rat toxicity. LD50(mol/kg)	Oral rat chronic toxicity (Log mg/kgbw/day)	Hepatotoxicity	Skin sensation	T.Pyriformis toxicity (Log µg/L)	Minnow toxicity (Log mmol/L)	Lipinski's rule Violation
Solanidine	2.596	1.334	YES	NO	0.378	-0.493	YES (1)
Solasodine	2.489	1.332	YES	NO	0.311	0.381	YES (1)
Solavetivone	1.643	1.19	NO	YES	1.453	0.874	YES (0)
Solafuranone	1.865	1.947	NO	YES	2.151	0.557	YES (0)
Scopoletin	1.95	1.378	NO	NO	0.516	1.614	YES (0)
N-p-trans-Coumaroyltyramine	2.17	1.271	NO	NO	1.008	1.514	YES (0)
Isofraxidin	2.326	1.825	NO	NO	0.431	1.862	YES (0)

Lauric acid	1.511	2.89	NO	YES	0.954	-0.084	YES (0)
β-sitosterol	2.552	0.855	NO	NO	0.43	-1.802	YES (1)
Diosgenin	1.921	1.452	NO	NO	0.399	0.247	YES (1)
Gabapentin	1.871	2.857	NO	NO	0.265	1.698	YES (0)

3.3. Interaction of Standard Drug (Gabapentin) with 5XVG

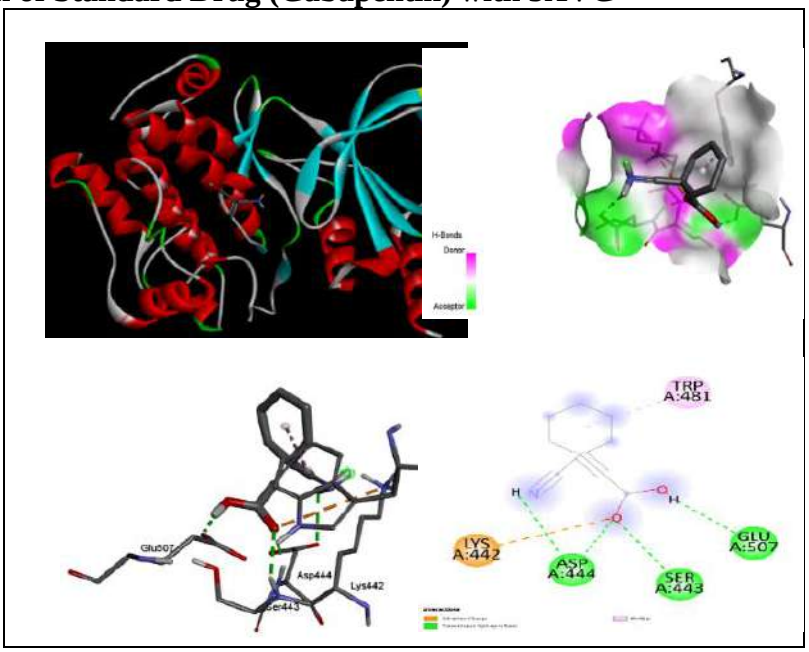
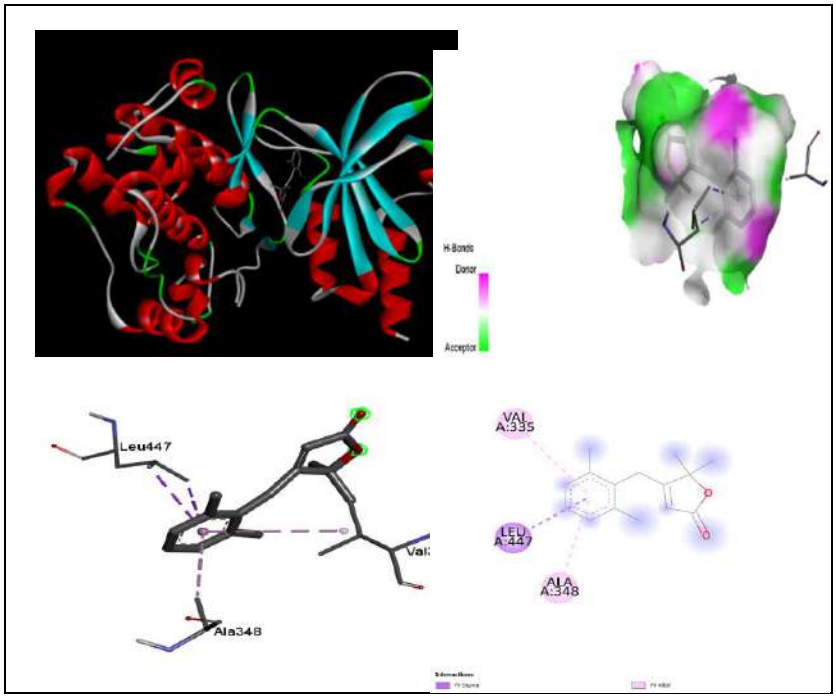


Fig. 2. Docking scores and binding interaction of Gabapentin (PDB ID: 5XVG). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

3.4. Interactions of phytoconstituents with 5XVG

A.Solafuranone



B.Isofraxidin

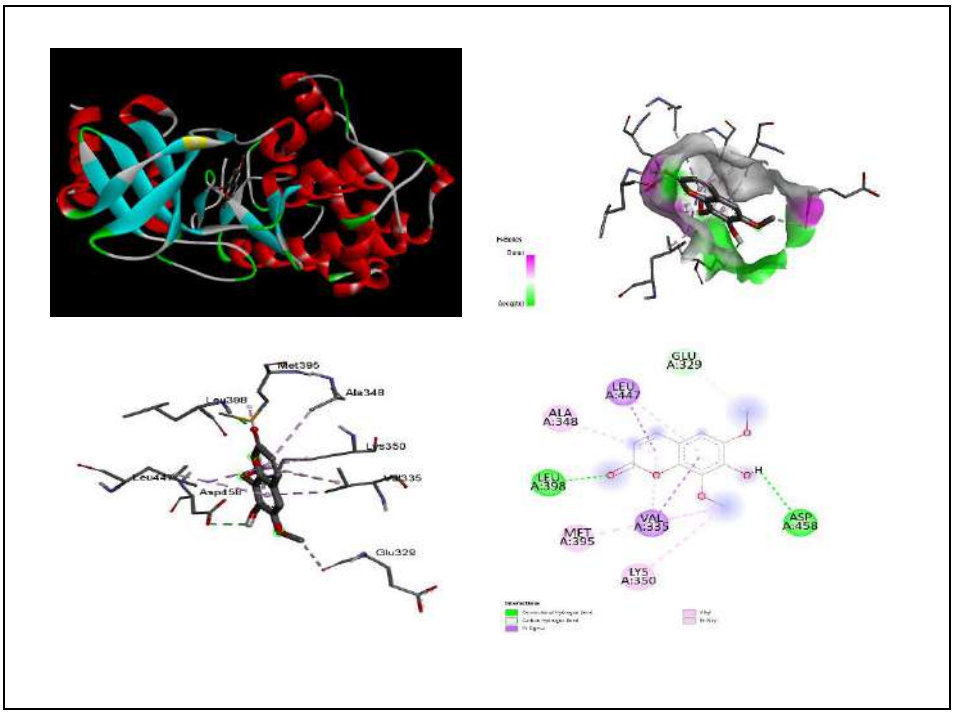


Fig. 3. Docking scores and binding interaction of phytoconstituents (PDB ID: 5XVG). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

3.5. Boiled Egg

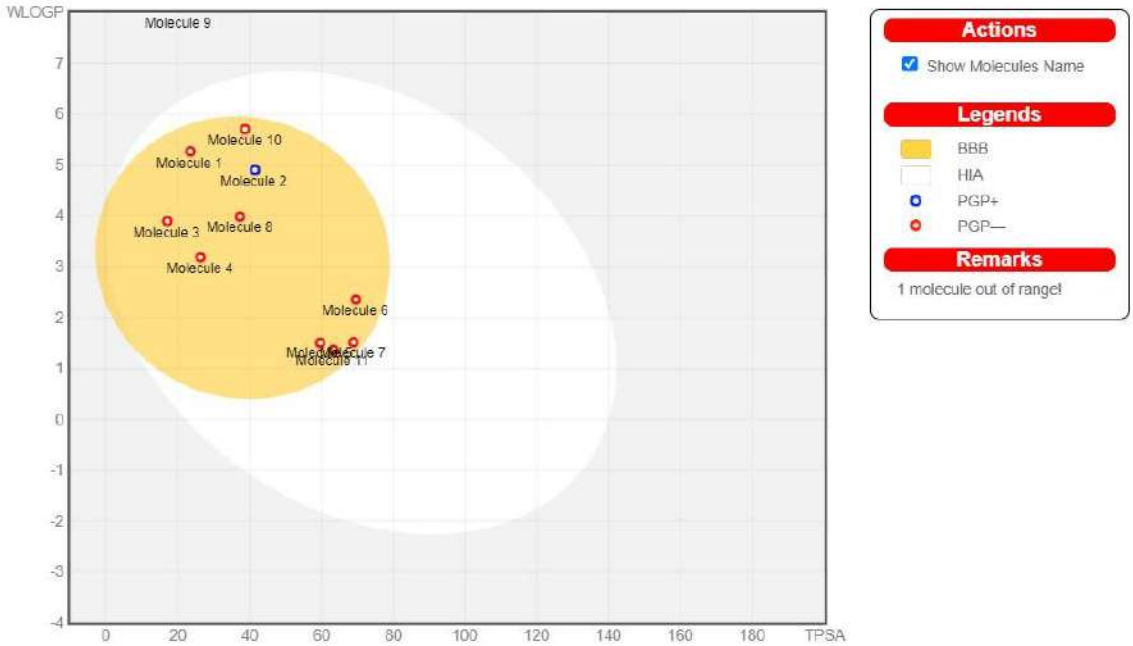


Fig no. 4. Combined Boiled Egg Diagram

Table no. 4. Name of molecules contained in Boiled Egg Diagram

MOLECULE NUMBER	MOLECULE NAME
1	Solanidine
2	Solasodine
3	Solavetivone
4	Solafuranone
5	Scopoletin
6	N-p-trans-Coumaroyltyramine
7	Isofraxidin
8	Lauric acid
9	β-sitosterol
10	Diosgenin
11	Gabapentin

BOILED means **B**rain **O**r **I**ntestina**L** **E**stimate**D** permeation predictive model. The boiled egg diagram shows two regions white region and yellow region.
The white region is the physicochemical space of molecules with highest probability of being absorbed by the gastrointestinal tract, and the yellow region (yolk) is the physicochemical space of molecules with highest probability to permeate to the brain.
In addition, the points are coloured in blue if predicted as actively effluxed by P-gp (PGP+) and in red if predicted as non-substrate of P-gp (PGP-).

4. CONCLUSION

In this study, we have carried out an *in-silico* screening of the phytoconstituents of *Solanum indicum* plant. This study demonstrated the sixteen compounds from *Solanum indicum* plant, (Solanidine, Solasodine, Solavetivone, Solafuranone, Scopoletin, N-p-trans-Coumaroyltyramine, Isofraxidin, Lauric acid, β-sitosterol, Diosgenin). The selected phytocompounds showed docking scores ranging from –8.3 to −4.2 kcal/mol in 5XVG. Among all, Solafuranone and Isofraxidin gave the highest binding energy (−8.1 kcal/mol) and (−6.8 kcal/mol) in complex with 5XVG, whereas the reference compound, Gabapentin showed a docking score with a binding energy of -5.1 kcal/mol. Furthermore, these ligands exhibited good ADMET properties. To summarize, phytoconstituents present in *Solanum indicum* possess strong effects against 5XVG and could be further evaluated for their antianxiety effect, as well as for the development of alternative drugs with fewer side effects for the treatment of stress.

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55

Computational Insight on the Argentophilic Interactions of Axially Chiral Ag-NHC Complex of *R*-BINOL Scaffold via TD-DFT

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Abstract

A fascinating interaction between the closed shells of many organometallic or inorganic compounds of d^8, d^2, and d^{10} systems is interestingly recognized as an important determinant of solid-state structures and a potential source of useful material properties. This work presents such kind of intramolecular metallophilic interactions in the X-ray diffraction structures of bimetallic Ag-NHC complex **1e**. The structural studies revealed that the geometry around the metal centers has M···M interactions. Time-dependent density functional theory (TD-DFT) experiments were done for complex **1e** to insight into the M···M and metal-ligand interactions in them. The results of computational and experimental studies of these complexes showed a good agreement with each other. This attracting feature of closed-shell metallophilic interactions is becoming extremely popular in a variety of materials including nanomaterials for their applications that include rewritable phosphorescent paper for use as color-switchable luminescent materials, phosphorescent organogels for reversible RGB-color switching, luminescence chemosensors to optoelectronic 'on-off' devices, etc.

Introduction

The new chiral ligand framework has been derived from inexpensive and readily available, enantiopure *R*-BINOL. This study uncovered some interesting cage-like structural features in the molecular structure of the silver complex that have potential applications in important domains like asymmetric catalysis and molecular recognition. Herein, we studied the intramolecular M···M interactions in the chiral bimetallic silver(I) NHC complex. In pursuing this work we followed similar steps and concepts which were conspicuously studied and reported in the literature for the silver(I) and gold(I) complexes of N/O-functionalized N-heterocyclic ligand exhibiting closed-shell $d^{10}\cdots d^{10}$ intermolecular argentophilic and aurophilic interactions.[1,2] Whereas, this work differs from the reported one, and includes investigations of the intramolecular argentophilic interactions in chiral NHC complexes of axially chiral scaffolds containing amido functions. This property of metallophilic interaction in materials is very much popular because of their various applications for *eg*. in chiral recognition, for the development of chiral polymeric materials,[3,4] in preparation of luminescent sensors[5,6] etc. Thus, the closed-shell metallophilic interactions by their subtle but significant influence have aroused interest in recent years and have made an impact in frontline application-oriented research.

Results and Discussion

Time-dependent density functional theory (TD-DFT) studies

As the molecular structure of the complex $[L(L'\text{-}NHC)_2]Ag_2$ (L = 2,2-dioxo-binapthyl, L' = phenyl-acetamido) (**1e**) is determined by X-ray diffraction studies (Figure 1) showed that these are monomeric-bimetallic in nature and exhibit close M···M contact of 3.3011(9) Å which is shorter than twice the *van der Waals* radii of the corresponding silver (3.44 Å), there by indicating the presence of closed shell $d^{10}\cdots d^{10}$ argentophilic interaction. Though numerous N-heterocylic carbene complexes of silver are known in literature are examples of structurally characterized discreet dimeric {(NHC)MX}2 (M =Ag, Au; X = halide)[7,8] type. But the

monomeric-bimetallic-*bis*-NHC complexes of type (Figure 1) exhibiting similar metallophilic interaction[84] are surprisingly not known to the best of our knowledge.

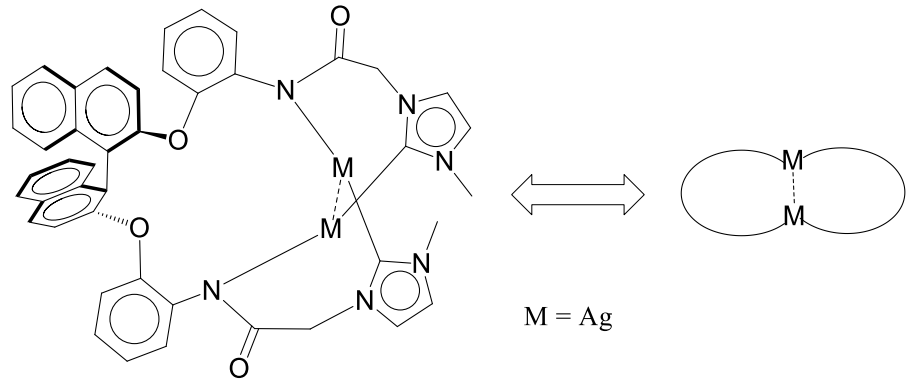
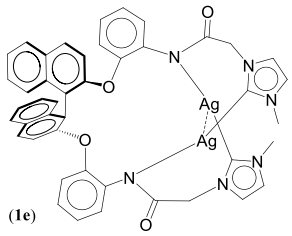


Figure 1. Monomeric chiral bis-M–NHC type of complex showing M···M interaction.

The geometry around the **1e** [C1–Ag1–N1] = 164.09(10)^o for **1e**, [C1–Ag1–N3] = 167.5^o is consistent with the linear geometries often observed for two-coordinated d^{10} metals.[9] Quite interestingly, a direct consequence of presence and absence of M···M (M = Ag) interaction occurring through the central metal atom (Ag1) in the monomeric-bimetallic complex is evidenced by the slightly bent angle [C1–Ag1–N1] = 164.09(10)^o at silver(I) in [L(L'-NHC)$_2$]Ag$_2$ (L = 2,2-dioxo-binapthyl, L' = phenyl-acetamido)[10] (**1e**) and these results suggest the presence of *argentophilic* interaction in complex **1e**. The effect is very weak as these frameworks are laid quite away from the metal binding sites of the ligands.

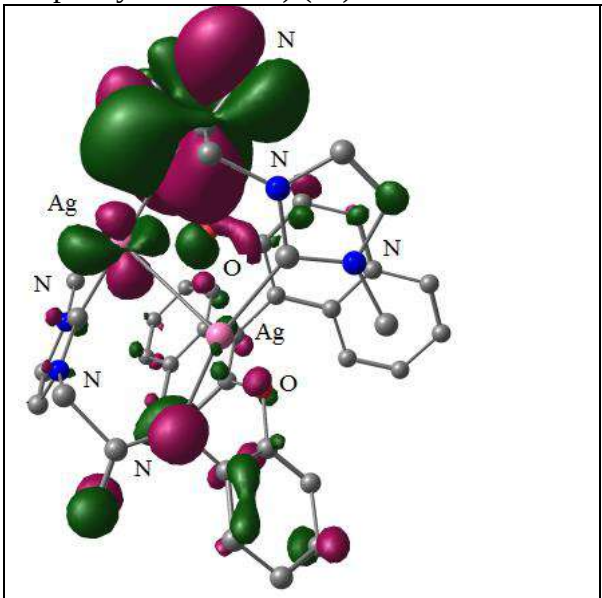
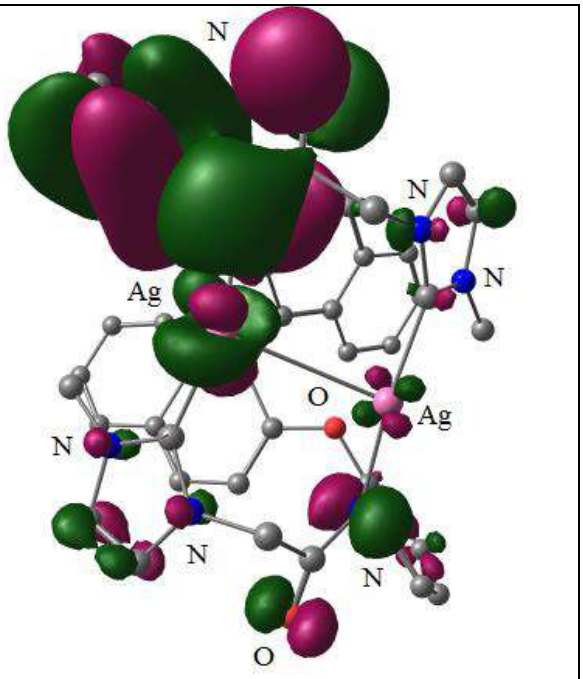
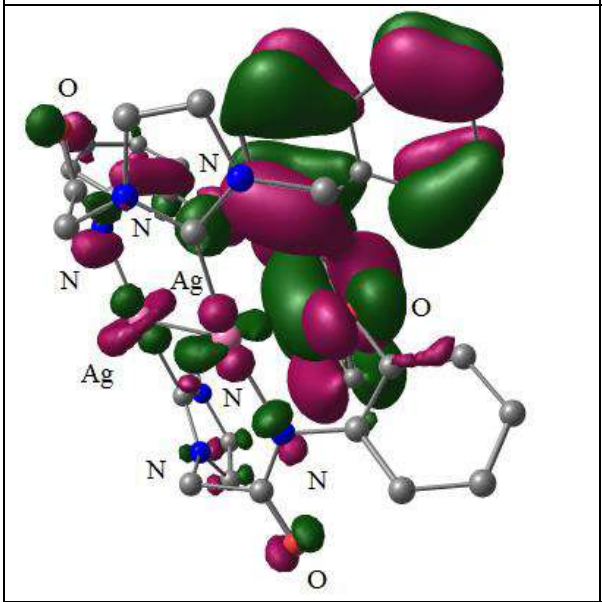
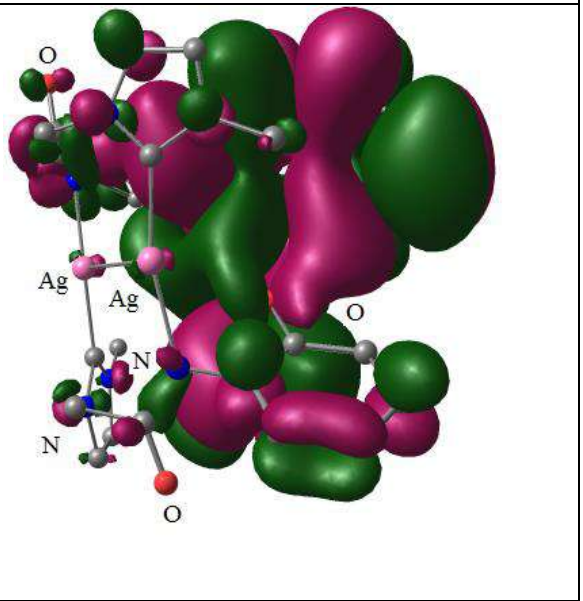
Table 1. Singlet excitation energies computed for complexes L(L'-NHC)$_2$]Ag$_2$ (L = 2,2-dioxo-binapthyl, L' = phenyl-acetamido) (**1e**) and L(L'-NHC)$_2$]Ag$_2$ (L = 2,2-dioxo-binapthyl, L' = phenyl-acetamido) **3e** at B3LYP/SDD, 6-31G* level of theory with an output are shown.

Complex	Excitation Wavelength (nm)	Oscillator strength	ψ_o-ψ_v	Transition coefficient	Type of transition
 (1e)	347.15	0.0905	HOMO→LUMO+1	0.6941	MLCT (π→π*)
	339.43	0.0061	HOMO→LUMO+2	0.7002	MLCT (π→π*)
	329.09	0.0064	HOMO→LUMO+3	0.6986	MLCT (π→π*)

Furthermore, to gain a better understanding about the interactions in the silver **1e** complex, and to obtain a deeper insight on the nature of NHC-metal interactions in these complexes, detailed density functional theory studies were carried using coordinates of the X-ray diffraction structure as an input data. In particular, the M···M bond order (Wiberg Indices) was computed using B3LYP/SDD, 6-31G(d) level of theory with the objective of estimating the strength of the closed-shell metallophilic interaction present in the complex. The computed bond order (Wiberg Indices) for the M···M interaction in the silver complex **1e** (0.1247) complex were approximately in the order of about a fourth of a single covalent thus supporting the evidence obtained from the X-ray diffraction analysis. The vertical transitions of the singlet excitation

energies obtained using TD-DFT calculations at the B3LYP/SDD, 6-31G(d) level of theory gives three transitions peaks for complex **1e** (347 nm, 339 nm, 329 nm) which coincides with the experimental results of UV-visible spectrum for **1e** and showed absorption at 340 nm.

Table 2. Selected molecular orbitals of the complex $L(L'\text{-}NHC)_2]Ag_2$ (L = 2,2-dioxo-binapthyl, L' = phenyl-acetamido) (**1e**) are shown.

	
HOMO Orbital # 203	HOMO Orbital # 204
	
HOMO Orbital # 205	LUMO Orbital # 206

TD-DFT study was performed on the geometry optimized computed structure, there can be a change in positions of transitions wavelengths, when the same experiments will be performed using X-ray crystallographic coordinates of the same complex. The number of transitions can also be increase by increasing the number of microstates in the experiment for the detailed study. These transitions obtained by the TD spectrum in **1e** complex has been assigned to the HOMO→LUMO π→π* MLCT transitions based on the comparison of intensities of the observed transitions and the comparable computed transitions along with their oscillatory

strength values[10] (Table 1). Different molecular orbitals which are associated with transitions of HOMO→LUMO for Ag-NHC complex **1e** (Table 2) are both ligand and metal in character.

Conclusions

Silver(I) complex **1e** showed mild range of metallophillic interactions in its structure. DFT studies performed on the complex **1e** showed good agreement with that of the experimental studies of the complex. These studies further followed by TD-DFT studies which enabled to determine the metal–metal and metal-ligand interactions, that also show different types of HOMO→LUMO transitions.

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56

Agricultural Influence and application of Mn(III), Fe(III) and VO(IV) Schiff base metal Complexes

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Abstract:
The newly synthesized complexes of Mn(III), Fe(III) and VO(IV) with Schiff base derived from 2-hydroxy-5-methyl acetophenone and 4-(p-hydroxyphenyl)-2-aminothiazole have been synthesized and characterized on the basis of elemental analysis, Infrared, ^{1}HNMR, molar conductance and magnetic susceptibilities. The Schiff base acts as a monobasic bidentate ligand commonly coordinates through the oxygen atom of phenolic -OH group and the nitrogen atom of azomethine group, which is confirmed by IR spectral data. Agricultural influence and application of Schiff base metal complexes.
Keywords: Schiff base, Magnetic susceptibility and Agricultural application

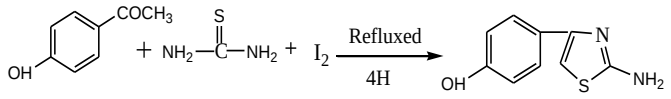
Introduction:

Schiff bases are considered to be the most versatile ligands as they form complexes with the metal atoms. Recent Advances in year 2023 the chiral Schiff Base Compounds[1] There is synthesis, characterization and biological activities of new Schiff Base Compound and its lanthanide complexe[2]. Antifungal Activity of Some Mixed Ligand Complexes Incorporating Schiff Bases[3] The aim of present investigation is to synthesize Mn(III), Fe(III) and VO(IV) metal complexes of Schiff base derived by the condensation of 2-hydroxy-5-methyl acetophenone and 4-(p-hydroxyphenyl)-2- aminothiazole and to check their potency towards various agricultural influence and application of Schiff base metal complexes.

Experimental:

All the chemicals were of A.R. grade and used as received. 2-hydroxy-5-methyl acetophenone (HMA) and 4-(p-hydroxyphenyl)-2 amino thiazole was prepared by known methods.[4 -7] The solvents were purified by standard methods.[8]

Synthesis of 4-(p hydroxyphenyl)-2 amino thiazole; A mixture of p-hydroxy acetophenone (12g), thiourea (15.2g), iodine (25g), and 60ml distilled water was taken in a 250ml R.B. flask. The mixture was refluxed for about 4h and poured into crushed ice to get the solid which is basify with sodium hydroxide. The product was filtered and crystallized from 70% ethanol, after several minutes the golden coloured product of 4-(p-hydroxyphenyl)-2 amino thiazole was separated out.[5 - 7] Yield: 10g (83.33%), m.p.: 216^{0}C



4-hydroxy acetophenone

4-(p -hydroxyphenyl)-2 amino thiazole

Synthesis of 2-hydroxy-5-methyl acetophenone 4-(p-hydroxyphenyl)-2 imino thiazole [HMAT]: A solution of 4-(p-hydroxyphenyl)-2 imino thiazole (0.02M) in 25ml of ethanol was added to an ethanolic solution(25ml) of 2-hydroxy-5-methyl acetophenone (0.02M) and the reaction mixture was refluxed on a water bath for 4h. After cooling a pale yellow coloured crystalline solid was separated out. It was filtered and washed with ethanol, crystallized from

DMF and dried under reduced pressure at ambient temperature. The purity of ligand was checked by elemental analysis and m.p. It was also characterized by IR and ^{1}H NMR spectral studies.
Yield: 60%; m.p. 310^{0}C

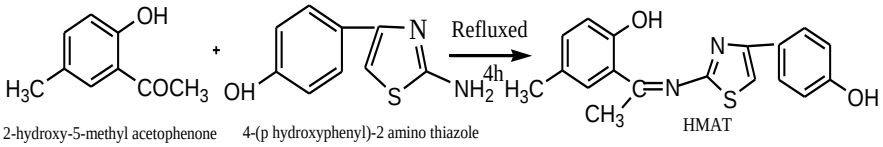


Table1. Analytical data of the Ligands.

Sr. No.	Ligand	Molecular Formula	Formula Weight	Colour and nature	Elemental Analysis		
					C% found (Cal.)	H% Found (Cal.)	N% Found (Cal.)
1.	HMAT	$C_{18}H_{16}N_2O_2S$	324.16	Yellow Crystalline	66.64 (66.75)	04.69 (04.93)	08.60 (08.63)

Preparation of complexes: All the metal complexes were prepared in a similar way by following method. To a hot solution of ligand HMAT (0.02M) in 25ml of ethanol a suspension of respective metal salts was added drop wise with constant stirring. The reaction mixture was refluxed on a water bath for 3-6 h. The precipitated complexes were filtered, washed with ethanol followed by ether and dried over fused calcium chloride. Yield: 45-55%
The complexes are soluble in DMSO and DMF but insoluble in water and common organic solvents. The metal chloride content of complexes were analyzed by standard methods.[9]
The ^{1}H NMR spectra of ligand was recorded and obtained from RSIC Chandigarh. IR spectra of the compounds were recorded on Perkin Elmer 842 spectrophotometer in the region 400-4000cm^{-1}, Carbon, Hydrogen and Nitrogen analysis were carried out at RSIC, Punjab University, Chandigarh. The molar conductance of the complexes at 10^{-3} M dilution in DMF were determined using equiptronic digital conductivity meter EQ-660 with a cell constant 1.00 cm^{-1} at room temperature. The magnetic moment measurement were made on a Gouy balance at room temperature using [$HgCo(SCN)_4$] as the calibrant.

Table 2. Analytical data and molar conductance of the compounds.

Compounds	Colour	Mol. wt.	Analysis % Found (calc.)					μ_{eff} B.M.	Λ_M (Ω^{-1} cm^2 mol^{-1})
			M	C	H	N	Cl		
$[MnL_2(OAc)]2H_2O$	Brown	796.1	6.73 (6.89)	57.10 (57.27)	4.52 (4.64)	7.00 (7.03)	_	4.3	22.2
$[FeL_2(H_2O)Cl]H_2O$	Brown	773.6	7.14 (7.22)	55.74 (55.84)	4.31 (4.39)	7.14 (7.23)	4.49 (4.58)	5.3	24.8
$[VOL_2]$	Green	713.2	7.11 (7.15)	60.45 (60.57)	4.09 (4.20)	7.76 (7.85)	_	1.55	10.8

Result and Discussion:
The ligand and its complexes have been characterized on the basis of ^{1}H NMR, IR spectral data, elemental analysis, molar conductance and magnetic susceptibility measurements data.
All these values and analytical data is consistent with proposed molecular formula of ligand. All the compounds are coloured solid and stable in air. They are insoluble in water but soluble

in coordinating solvents like DMF and DMSO. The molar conductance values in DMF(10^{-3} M) solution at room temperature (Table 2) shows all the complexes are non electrolytes.
The ^{1}H NMR spectra of the ligand shows signals at δ 12.03, (1H, s phenolic OH), δ 9.00 (1H, s, phenolic OH), δ 6.83, 6.82, 6.81 and 6.80 (4H, m, phenyl) δ 7.58, 7.53, and 7.52 (3H, s Phenyl), 6.49 (1H s thiophene), and 2.92(3H, s, methyl) 2.58 (3H, s, methyl)[10-13]. The IR spectral data of the ligand and its metal complexes are given in Table 3. The IR spectrum of the free ligand exhibits a broad band at 3119 cm^{-1} which is ascribed to ν(O-H) vibration lowered due to intramolecular O-H·····N hydrogen bonding. The absence of C=O band at around 1700 – 1750 cm^{-1} indicates the Schiff base formation.[14-17] The other bands at 1620, 1513 and 1121 are assignable to ν(C=N), ν(C-O)(phenolic) and ν(C-S). In the spectra of all the complexes the ν(C=N) band is lowered by 25-40 cm-1 indicating the involvement of azomethine nitrogen in coordination. Also, the band due to ν(O-H) of the ligand disappeared indicating the coordination of phenolic oxygen to metal ion via deprotonation. This is also supported by the shift in ν(C-O) (phenolic) mode. IR spectrum of Mn(III) complex display two bands near 1616, 1446 cm^{-1} assigned to ν_{asy}(OCO) and ν_{sym}(OCO) respectively, indicating monodentate nature of the coordinated acetate group. The strong IR bands around 960, 1156 and 910 in the spectrum of VO(III), are assigned to ν(V=O) ν(Zr-OH) ν(O=U=O) vibrations.

Table 3. IR spectra of ligand and metal complexes:

Compound	*V*(O-H) hydrogen bonded	*V*(C=N) Imine	*V*(C-O) phenolic	*V*(M-O)	*V*(M-N)
HMAT	3119	1620	1513	-	-
$[MnL_2(OAc)]2H_2O$	_	1560	1450	500	425
$[FeL_2(H_2O)Cl]H_2O$	_	1590	1502	520	455
$[VOL_2]$	_	1594	1508	515	450

Agricultural Influence and application of metal complexes: A ploughshare is an cobalt Copper and nickel metal complexes used in agriculture to increase the production of crops. They are used prior to the seedling stage to loosen up the soil. Essential observed that cobalt (Co), copper (Cu), iron (Fe), manganese (Mn), molybdenum (Mo), nickel (Ni), and zinc (Zn) complexes with schiff base plays a beneficial role in plant growth and development. Synthetic Action on Insecticides: Schiff base ligand was derived from the condensation of thiazole and 2-hydroxy-5-chloro-3-nitro acetophenone. Their metal complexes show high activity against insects[18]. 2-amino-4-phenylthiazole acts as intermediate in synthesis of photostable pyrthriod insecticides[19]. Flourination on aldehyde part of Schiff base increases insecto acracicidal activity[20]. Schiff bases and their metal complexes with Mn(III), Fe(III) and VO(IV) show insecticidal activities against bollworm [21]. Most metals complexes cause environmental and atmospheric pollution, and may be lethal to humans. Heavy metals can become strongly toxic by mixing with different environmental elements, such as water, soil, and air, and humans and other living organisms can be exposed to them through the food chain. Arsenic, cadmium, chromium, copper, nickel, lead and mercury are the most common metals which can pollute the environment. They are not all equally important but all play a role in plant growth. The heavy metals Mn(III), Fe(III) and VO(IV) are micronutrients or trace elements for plants. They are essential for growth and stress resistance as well as for biosynthesis and function of different biomolecules such as carbohydrates, chlorophyll, nucleic acids, growth chemicals, and secondary metabolites. Nitrogen (N) containing Schiff base metal complexes is made

available to the plant from the air and soil. But most of the needed elements that are nutrients for plants come from the soil.

Conclusions: The Schiff bases ligand and their metal complexes shows more activity towards the agricultural Influence and applicable for plant growth.

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57

Recent Applications of Deep Eutectic Solvent (DES), a Greener Media in Organic Synthesis

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Abstract: A modern era of research mainly focused on study of use of solvent in organic transformation, with its advantageous as environmental benign, cost effectiveness and in a simple and sophisticated practical term. In the search of safe, non-toxic, cheap, biorenewable and biodegradable solvents, deep eutectic solvents (DESs) get the prominent position. DES acts as a valuable alternative which overcome the limitations of use of traditional volatile organic compound (VOCs) solvents. This review paper aims to inspire scientists, work in organic field to study the potential of DES. From understanding of the different aspects like effect of temperature, concentration, addition of water etc. would provide knowledge for deciding the scheme of organic synthesis. Review paper includes study of various organic reactions from literature using DESs as catalyst and solvent media in a tabular form. It also includes recycling and reuse of DESs in organic reactions. Convenient reaction set-up, simple separation and purification built impact of DESs in laboratory and industry in near future.

Keywords: Deep eutectic solvent, catalyst and solvent media, green/ecofriendly solvent, organic transformation, recycle and reuse.

1. Introduction

"Protecting our common environment" is the key objective given in Millenium Declaration adopted by United Nations in 2000. From the last decades when we throw a light on our changing lifestyle which becomes more demanding in different fields like drugs, plastic, polymer etc. These demand causes damage and exploitation of natural resources like water, petroleum, air, minerals etc and the question was arises '*Why is chemical manufacture becoming unsustainable?*'[1]. Now it becomes needed to make balance between increasing demand in production of chemical compounds with safe and clean environment. Amongst three states of matter, the most convenient reaction media is solvent (liquid state). Most common volatile organic compound (VOCs) solvents, due to their high cost, high toxicity, high inflammability, non-biodegradability and causing negative impact on environment[2], there is need to develop a new concept of "*ideal green solvent*". In search of ideal solvents, water, supercritical carbon dioxide (SCD) [3] supercritical water (SCW)[4], and ionic solvents [5] are discovered but due to their disadvantages under different reaction conditions make them unsuitable solvent as reaction media for industrial purpose. Abbott in 2003 [6] first introduced a new generation of safe, nontoxic, cheap, biorenewable and biodegradable, sustainable designer solvent [7] termed as "*Deep Eutectic Solvent*" (DES). They exhibit similar properties like ILs as they work on similar molecular base but still more superior than Ionic liquids. As a designer and environmentally benign solvent, DES has numerous applications in various fields. There are many reviews to study organic reactions based on greener approach using DESs as reaction media. That encourages us to study organic reactions using greener solvent DES.

This review article includes general introduction of DESs, classification and types of DESs, applications in various fields and study of various organic reactions using DESs as

catalyst and solvent media. This review also discussed optimized reactions with recycling and reuse of DESs in organic reactions from literature published in between the session 2020-2023.

2. Deep Eutectic Solvents (DESs)

Deep Eutectic Solvents (*DESs*), also known as *Deep Eutectic Ionic Liquids* (*DEILs*)[8], *Low Melting Mixtures* (*LMMs*) or *Low Transition Temperature Mixtures* (*LTTMs*)[9] in the literature. The first reported DES was a mixture of choline chloride and urea (1:2), with a melting temperature of 12 ºC, much lower than those of the starting materials, 302 ºC and 133 ºC, respectively [10]. DES is generally defined as a binary mixture of an ionic components, one is a hydrogen bond acceptor (HBA) like chloride ion and the other a hydrogen bond donor (HBD), such as an alcohol, amide or carboxylic acid. Simply DES is a neoteric solvent [11] which are able to form a new eutectic phase (which is a liquid below 100 °C) through hydrogen-bond-promoted self-association and no covalent compounds are formed between them, hence the term '*Deep*' is used [12,13].

3. Types and Classification of DESs

DESs are broadly classified as Hydrophilic and Hydrophobic DESs. Main difference between them is their melting point depression. Hydrophilic DESs have deep depression in freezing point due to extensive hydrogen bond interaction eg. choline chloride salt with small alkyl chains, acids, amines etc. While hydrophobic DESs have a large and small depression in freezing point eg. Long hydrocarbon alkyl chain containing salts and acid like Decanoic acid, Dodecanoate sodium salts etc.

DESs are also classified into four types (table 1) from numerous possible combinations of HBD and HBA components. Marcus [14] reported data regarding their molecular mass and their eutectic melting points. Nonionic deep eutectic solvents are the other class of DESs, introduced by Francisco *et al* [15,16] originated from Type –III DES and are characterized by low iconicity, having low electrical conductivity.

Table 1. Types of eutectic mixtures

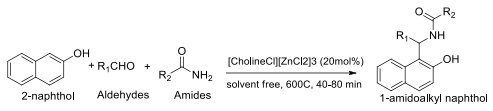
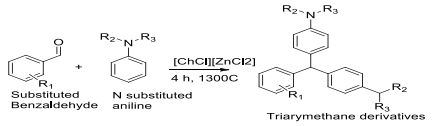
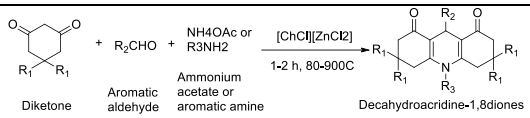
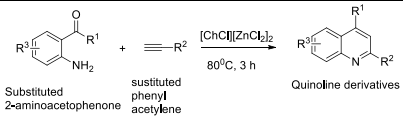
Types	General formula	Terms	Example
DES I	$Cat^+X^-+zMCl_x$	M=Zn, In, Sn, Al, Fe	$ChCl+ZnCl_2$
DES II	$Cat^+X^-+zMCl_x$	M=Cr, Ni, Cu, Fe, Co	$ChCl+CoCl_2.6H_2O$
DES III	Cat^+X^-+zRZ	Z=OH, COOH, $CONH_2$	ChCl+urea
DES IV	MCl_x+zRZ	M=Zn, Al and Z=OH, $CONH_2$	$ZnCl_2$+urea

4. Various Organic reactions in four types of deep eutectic solvents

4.1 *DES Type I catalysed organic reactions*

DES type –I is the combination of quaternary ammonium salts with metal chlorides, eg. quaternary ammonium salts forms eutectic mixtures with zinc and tin chloride to result in freezing points between 13 and 92 °C [17] respectively.

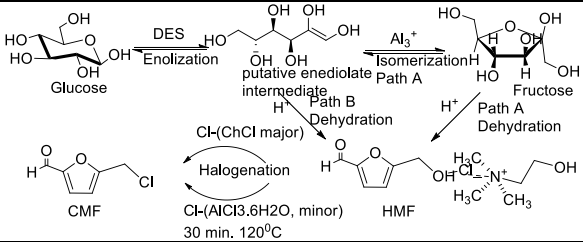
Table 2. DES type I reactions

S. N.	DES used	General reaction and reaction condition	Scope of reaction (%yield)	No. of recycle of DES	References
1.	[CholineCl] $[ZnCl_2]_3$		45-95%	3	[18]
2.	[ChCl][$ZnCl_2$]		30-81%	5	[19]
3.	[ChCl][$ZnCl_2$]		75.1-92.6%	3	[20]
4.	[ChCl][$ZnCl_2$]$_2$		63-98%	-	[21]

4.2 *DES Type II catalysed organic reactions*

DES type II involves organic salts that are easy to handle and overcomes moisture absorption problem in DES type I. Eg. Choline chloride forms a deep eutectic solvent with calcium chloride hexahydrate at several molar ratios, at a 1:2 molar ratio, melting point 2.70 ºC [22].

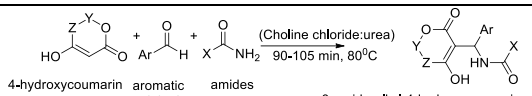
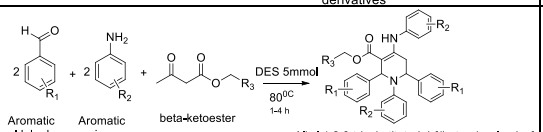
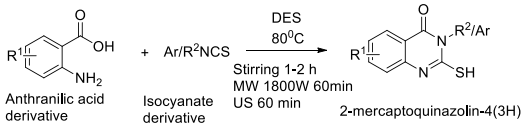
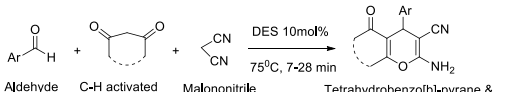
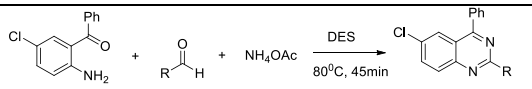
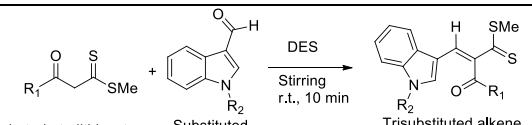
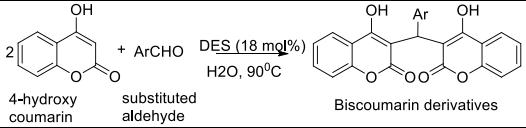
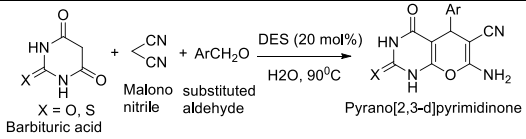
Table 3. DES type II reactions

S. N.	DES used	General reaction and reaction condition	Scope of reaction (%yield)	No. of recycle of DES	References
1.	$ChCl.AlCl_3$ $.6H_2O$		29-86%	10	[23]

4.3 *DES Type III catalysed organic reactions*

Type III DESs are very attractive and most investigated class of DES as they are composed of biodegradable and non-toxic HBD's like urea, organic carboxylic acids, polyols. Eg. Tetrabutylammonium chloride forms deep eutectic solvents with ethylene glycol (1:3 mole ratio), glycerol (1:4 mole ratio), and triethylene glycol (1:3mole ratio) with eutectic freezing point −31 °C, −13 °C and −43 °C, respectively [24].

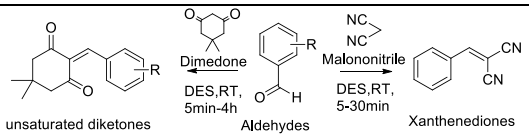
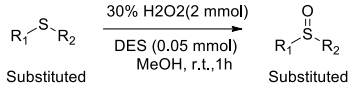
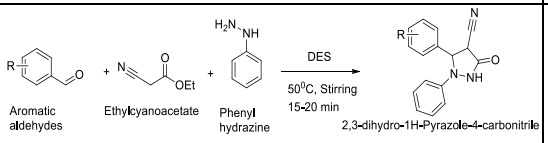
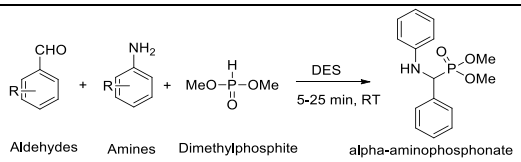
Table 4. DES type III reactions

S. N.	DES used	General reaction and reaction condition	Scope of reaction (%yield)	No. of recycle of DES	References
1.	CholineCl:Urea		84-92%	4	[25]
2.	EthyltriphenylphosphoniumbromideTHFtetracarboxylic acid.		60-95%	5	[26]
3.	ChCl:Urea (1:2)		Stir.(20-76)MW(12-49) US(17-64%)	4	[27]
4.	[ChCl][Gabapectine]		86-95%	5	[28]
5.	ChCl:Urea (1:2)		84-97%	4	[29]
6.	ChCl:Urea (1:2)		84-90%	5	[30]
7.	Taurine/choline chloride		87-95%	4	[31]
			88-94%		

4.4 *DES Type IV catalysed organic reactions*

Organic salts used in DES type I, II and III as HBA are now replaced by metal halides in DES type IV. Urea:$ZnCl_2$ (3.5:1mole ratio) forms a DES with a melting point of 9 °C [32].

Table 5. DES type IV reactions

S. N.	DES used	General reaction and reaction condition	Scope of reaction (%yield)	No. of recycle of DES	References
1.	$CeCl_3 \cdot 7H_2O$/ urea (1:5)		Diketone(80-96%)Xanthenedione (88-97%)	5	[33]
2.	$ZrOCl_2 \cdot 8H_2O$/ Urea (1:5)		91-99%	3	[34]
3.	K_2CO_3/Glycerol (1:4)		85-95%	-	[35]
4.	$ZrOCl_2 \cdot 8H_2O$: Urea (1:5)		88-98%	5	[36]

5. Conclusion

DESs have aroused increasing scientific attention in the field of greener chemistry due to their easy availability and cost effectiveness. Study of organic reactions under four types of DESs, may inspire scientists, who work in organic field to glimpse the potential of DESs. So far, from the study of many reactions, it was observed that reaction in DES along with additional greener methods like microwave irradiation or ultrasonication also helps to increase efficiency and productivity of reactions. It is observed that viscosity plays a very important role in DESs to act as organic solvent. Miracle of DESs in many organic reactions is its recyclability and its reuse, without loss of its activity many times without formation of side products which may affect yield of pure product. Literature study reveals, increase in product yield, higher reaction rates, and reduce reaction time and no need of further purification of product using thin layer chromatography, as compared with the conventional organic synthetic route. On comparison of four types of reactions in DESs media, DESs Type III is mostly used in many organic transformations, while DES Type II is very rarely used as reaction media. Thus still

further research is needed to study mechanism involved in organic transformation involving DESs as reaction solvent. From environmental point of view in an area of organic chemistry, applications of DESs as reaction media, is getting more importance every day and their viewpoint in both laboratory and industry may opens a new era in organic synthesis. But beside of enormous green applications of DESs the next step will be focused on study of its toxicity.

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58

Synthesis, Characterization and Pharmacological Evaluation of Some New Functionalized Flavone Derivatives From B-Diketones

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ABSTRACT: In present work, a series of novel flavone analogues have been synthesized by dehydrative cyclization of 1,3-diketone (β-diketone) derivatives carrying p-chloro-m-cresol moiety under acidic condition and characterized by usual chemical characteristics, elemental analysis, IR, ^{1}H NMR and Mass spectral data studies for structure assignment. All the newly synthesized compounds were screened for their *in vitro* antimicrobial activities against human pathogenic bacterial and fungal strains by disc diffusion method. Moreover, they have been evaluated for their *in vitro* antioxidant and anti-inflammatory properties by DPPH free radical scavenging and inhibition of protein denaturation methods respectively with reference to standard drugs.
Keywords: Flavone, β-diketone, p-chloro-m-cresol, synthesis, pharmacological evaluation.

INTRODUCTION

Flavonoids (from the Latin word flavus, which means 'yellow') are a large group of natural polyphenolic compounds with low-molecular weight; particularly, they belong to a class of plants secondary metabolites widely found in fruits, vegetables and plants derived beverages such as green tea and wine. Flavonoids are associated with a broad spectrum of health-promoting effects and are an indispensable component in a variety of nutraceuticals, pharmaceuticals, medicinal and cosmetic applications because of their oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties coupled with their capacity to modulate key cellular enzyme functions. Structurally, flavonoids is 2-phenyl benzo-γ-pyrone (2-phenyl chromone) consists of fifteen basic carbon atoms (C6–C3–C6) with a general formula $C_{15}H_{10}O_2$ and classified into six subclasses on their chemical structure[1] among which flavone is the most prominent class of flavonoids based on the backbone of 2-phenyl-4*H*-chromen-4-one (2-phenyl-1-benzopyran-4-one). Flavones are heterocyclic polyphenolic compounds ubiquitously present in plant kingdom, especially in seeds, citrus fruits, olive oil, tea and red wine, vegetables, nuts, stems and flowers, honey and are commonly consumed with the human diet. Flavones display a broad spectrum of biological properties, including antibacterial[2], antifungal[3], antiviral[4], antidiabetic[5], anti-inflammatory[6-7], antioxidant[8-9], hepatoprotective[10], anticancer[11], anti-tubercular[12], antitumoral[13], and antimalarial[14] activities, making them an attractive target for synthesis and further study. Number of methods have been developed for the synthesis of flavones and its derivatives[15-17], among them Claisen-Schmidt condensation and Baker-Venkataraman rearrangement (BVT) are traditional methods to made flavones[18]. Under Claisen-Schmidt conditions, hydroxychalcones produced from 2-hydroxy-acetophenone and benzaldehyde can undergo oxidative cyclization to yield flavone rings. In Baker-Venkataraman approach[19-20], 2-hydroxyacetophenones are converted into benzoyl esters, which are rearranged by a base to a 1,3-diphenylpropane-1,3-diones (which exist also in equilibrium with their enolic forms) followed by cyclization under acidic condition to yield flavones.

In view of pharmacological significance of flavones and in continuation of our work on synthesis of derivatives of β-diketone, it was decided to prepare some novel flavone analogues

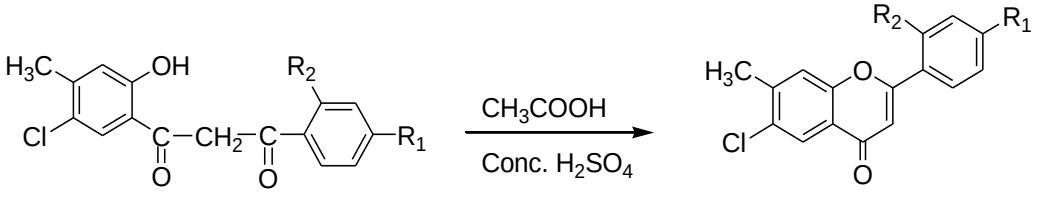
through cyclodehydration of 1,3-diketones (β-diketones) and to study their pharmacological properties. Initially, the 5-chloro-2-hydroxy-4-methylacetophenone (2) was prepared by an acetylation of p-chloro-m-cresol (a) followed by Fries rearrangement of p-chloro-m-cresyl acetate (1) with anhydrous $AlCl_3$. Then 2-benzoyloxyacetophenones (3a-d) were synthesized by condensation of 5-chloro-2-hydroxy-4-methylacetophenone (2) with appropriate aromatic carboxylic acids in pyridine using $POCl_3$. The required starting materials were prepared via Baker-Venkataraman transformation (BVT) wherein 2-benzoyloxyacetophenones (3a-d) were treated with base (KOH/pyridine) to form β-diketones namely 1-(5'-Chloro-2'-hydroxy-4'-methylphenyl)-3-(substituted phenyl) propane-1,3-diones (4a-d)[21]. In this, all the synthesized diketones containing p-chloro-m-cresol moiety on dehydrative cyclization in glacial acetic acid and H_2SO_4 to yield the titled compounds (5a-d). The success of the synthesis and constitutions of synthesized compounds have been confirmed through their melting point, TLC, elemental analysis, IR, ^{1}H NMR and Mass spectral studies. Moreover, they have been evaluated for their antimicrobial, antioxidant and anti-inflammatory properties by known literature methods.

MATERIALS AND METHODS

All the chemicals used were of synthetic grade. Melting points were taken in open glass capillaries and were uncorrected. All the compounds were purified by recrystallization and their purity was monitored by TLC using Silica gel (G) plates. Elemental analyses were carried out with a Thermo Scientific (Model FLASH 2000) instrument. IR spectra were recorded on Shimadzu (Model IR Afinity-1CE) spectrophotometer using KBr pellets. A Bruker (Model Avance Neo) FTNMR 500 MHz spectrometer was used to acquire ^{1}H NMR spectra with DMSO-d_6 as the solvent and TMS as an internal fashionable. Meanwhile, mass spectra were recorded on Waters Micromass (Model Alliance 2795 Q-TOF) spectrometer.

General procedure for the synthesis of flavone derivatives (5a-d)[22]

To a solution of 1-(5'-Chloro-2'-hydroxy-4'-methylphenyl)-3-(substituted phenyl) propane-1,3-diones (4a-d) (0.025 M) in glacial acetic acid (30 ml), sulphuric acid (5 ml) was added. The content of reaction mixture was refluxed on water bath for 2 hr followed with occasional stirring. The reaction mixture was allowed to cooled at room temperature and poured into crushed ice to precipitate the product. The separated product was filtered, washed with water followed by sodium hydrogen carbonate (10%) solution and then with sufficient cold water until the washings were neutral to litmus**.** The dried product was recrystallized from hot ethanol to get shiny yellow crystals of flavones (5a-d) as desired products (Figure-1).



(4a-d) (5a-d)

Where, 4a, 5a : R_1= NO_2 ; R_2= H 4c, 5c : R_1= Cl ; R_2= H
4b, 5b : R_1= Br ; R_2= H 4d, 5d : R_1= Cl ; R_2= Cl

Figure-1: Scheme for the synthesis of the flavone derivatives (5a-d)

Pharmacological Evaluation
Antimicrobial activity

All the newly synthesized flavones (5a-d) were screened for their *in vitro* antimicrobial sensitivity against *Escherichia coli* (gram -ve), *Staphylococcus aureus* (gram +ve) bacterial strains and *Aspergillus niger*, *Candida albicans* fungal strains by disc diffusion method[22-25]. Mueller-Hinton agar (MHA) and Potato Dextrose agar (PDA) plates were employed as culture medium respectively for bacterial and fungal sensitivity and DMSO was used as solvent control. Ofloxacin and amphotericin were used as standard drugs for antibacterial and antifungal activities respectively. The compounds were dissolved in DMSO to give 100 µg/ml, 250 µg/ml, 500 µg/ml solutions. Sterile filter paper discs (Whatmann filter paper No. 40) of 10 mm diameter were dipped in these solutions, dried, and placed on nutrient agar plates spreaded with the bacteria and fungi. The plates were further incubated for 24 hr at 37 ^{0}C for antibacterial and 72 hr at 28 ^{0}C for antifungal testing and the zones of inhibition were measured in mm using antibiotic zone reader (Hi-Media).

Antioxidant activity

The *in vitro* antioxidant activity of synthesized compounds was performed based on DPPH radical-scavenging assay with free radical scavenging effect of the stable 2, 2-diphenyl-1-picrylhydrazyl (DPPH) with slight modifications[26-29]. A stock solution of DPPH (1.3 mg/ml) was prepared by dissolving 13.0 mg in 10 ml of methanol. The stock solutions of test compounds (5a-d) (100 µg/ml) were prepared and further diluted to prepare solutions of various concentrations (10, 20, 30, 40 and 50 µg/ml). Similarly, a stock solution of standard ascorbic acid (1 mg/ml) was prepared by dissolving 10 mg ascorbic acid in 10 ml of methanol. From this stock solution further dilutions of various concentrations (10, 20, 30, 40, and 50 µg/ml) were prepared. Further, 1 ml of DPPH solution was mixed with 1 ml of different concentration of test solutions and standard (ascorbic acid). These solutions were kept for 30 min in dark and absorbance was measured at 517 nm using methanol (5 ml) with DPPH solution (1 ml) as blank (positive control). The percentage of scavenging activity was calculated by following formula:

% Scavenging = [Abs. of control–Abs. of test sample/Abs. of control] × 100

Anti-Inflammatory activity

The *in vitro* anti-inflammatory activity of synthesized compounds was performed by employing inhibition of protein denaturation assay[30]. Stock solution of NSAID ibuprofen as a reference drug (positive control) was prepared by dissolving 10 mg of ibuprofen in 10 ml of distilled water. Serial dilution from above stock solution takes 0.1 ml, 0.2 ml, 0.3 ml, 0.4 ml, 0.5 ml and prepare 10 ppm, 20 ppm, 30 ppm, 40 ppm, 50 ppm and also it was performed for four sample extract (5a-d). All samples contain 5 ml of total volume. Reaction mixtures were prepared using 2.8 ml of phosphate-buffered saline (pH 6.4) and 0.2 ml of egg albumin. Then take 2 ml of extract from each different concentration were mixed gently with reaction mixtures. A similar procedure was used for reference drug ibuprofen. The absorbance of these solutions was determined by spectrophotometer at wavelength of 660 nm. The percentage inhibition of protein denaturation was calculated by following formula:

% Inhibition = [Abs. of blank – Abs. of test sample/Abs. of blank] × 100

RESULTS AND DISCUSSION

Spectral data analysis

The structures of all the newly synthesized flavones (5a-d) were characterized on the basis of melting point, TLC, elemental analysis, IR, ^{1}H NMR and Mass spectral studies. The IR, ^{1}H NMR spectra showed expected signals corresponding to various groups present in each of the compounds. The mass spectrum of all the compounds were found to in full agreement with the proposed structures and showed expected peaks which confirms the molecular weights of compounds. The spectral and physical data (Table-1) of all the compounds are shown below:

(5a): 2-(4'-Nitrophenyl)-6-chloro-7-methyl-4*H*-chromen-4-one: IR (cm^{-1}, KBr): 3085 [C-H stretch (aromatic)], 2930 [C-H stretch in $-CH_3$ (aliphatic)], 1647 (C=O stretch), 1525 [C=C stretch (aromatic)], 1431 [$-NO_2$ stretch (asym.)], 1345 [$-NO_2$ stretch (sym.)], 1247 (C-O stretch), 655-691 (C-Cl stretch); ^{1}H NMR (DMSO-d_6/500 MHz): δ 2.5 ppm (s, 3H of $-CH_3$), δ 3.38 ppm (s,1H of -C=CH- of flavone), δ 7.9-8.4 ppm (m, 6H of Ar-H); MS (m/z): 316.04(M^+).
(5b): 2-(4'-Bromophenyl)-6-chloro-7-methyl-4*H*-chromen-4-one: IR (cm^{-1}, KBr): 3046 [C-H stretch (aromatic)], 2924 [C-H stretch in $-CH_3$ (aliphatic)], 1632 (C=O stretch), 1434 [C=C stretch (aromatic)], 1244 (C-O stretch), 648 (C-Br stretch); ^{1}H NMR (DMSO-d_6/ 500 MHz): δ 2.5 ppm (s, 3H of $-CH_3$), δ 3.4 ppm (s,1H of -C=CH- of flavone ring), δ 7.8-8.1 (m, 6H of Ar-H); MS (m/z): 348.96/350.96 (M^+).
(5c): 2-(4'-Chlorophenyl)-6-chloro-7-methyl-4*H*-chromen-4-one: IR (cm^{-1}, KBr): 3043 [C-H stretch (aromatic)], 2922 [C-H stretch in $-CH_3$ (aliphatic)], 1724 (C=O stretch), 1438 [C=C stretch (aromatic)], 1254 (C-O stretch), 725 (C-Cl stretch); ^{1}H NMR (DMSO-d_6/ 500 MHz): δ 2.5 ppm (s, 3H of $-CH_3$), δ 3.4 ppm (s,1H of -C=CH- of flavone ring), δ 7.6-8.1 ppm (m, 6H of Ar-H); MS (m/z): 305.02 (M^+).
(5d): 2-(2',4'-Dichlorophenyl)-6-chloro-7-methyl-4*H*-chromen-4-one: IR (cm^{-1}, KBr): 3284 [C-H stretch (aromatic)], 2928 [C-H stretch in $-CH_3$ (aliphatic)], 1635 (C=O stretch), 1427 [C=C stretch (aromatic)], 1103 (C-O stretch), 628 (C-Cl stretch); ^{1}H NMR (DMSO-d_6/ 500 MHz): δ 2.5 ppm (s, 3H of $-CH_3$), δ 3.34 ppm (s,1H of -C=CH- of flavone ring), δ 7.0-8.1 (m, 5H of Ar-H); MS (m/z): 338.99 (M^+).

Table-1: Physical and analytical data of synthesized substituted flavones (5a-d)

Compound code	Molecular Formula	Mol.wt (g/mol)	m.p. (^{0}C)	% Analysis: Found (Calcd.)			Yield (%)	R*f* value
				C	H	Cl		
5a	$C_{16}H_{10}ClNO_4$	315.71	160-162	61.08 (60.87)	3.06 (3.19)	11.30 (11.23)	80	0.64
5b	$C_{16}H_{10}BrClO_2$	349.61	166-169	55.29 (54.97)	2.79 (2.88)	(9.86) (10.14)	78	0.68
5c	$C_{16}H_{10}Cl_2O_2$	305.16	156-158	63.67 (62.97)	3.79 (3.30)	21.99 (23.24)	88	0.70
5d	$C_{16}H_9Cl_3O_2$	339.60	170-172	56.77 (56.59)	2.81 (2.67)	(31.16) (31.32)	92	0.69

Pharmacological activity

The antibacterial and antifungal activities of all the newly synthesized compounds were examined *in vitro* tests. The resulting data on antimicrobial activities are depicted in Table-2 and Table-3. They were further subjected for their *in vitro* antioxidant and anti-inflammatory activity whose results are summarized respectively in Table-4 and Table-5 and also shown in Figure-2 and Figure-3 statistically.

Table-2: Antibacterial activity of newly synthesized flavone derivatives (5a-d)

Compound code	Zone of inhibition in mm							
	Escherichia coli (Gram -ve)				*Staphylococcus aureus* (Gram +ve)			
	Concentration of compounds (µg/ml)				Concentration of compounds (µg/ml)			
	100	250	500	Std.	100	250	500	Std.
5a	NI	NI	NI	20 mm	NI	NI	NI	22 mm
5b	NI	NI	NI		NI	NI	NI	

5c	NI	NI	NI		NI	NI	NI	
5d	10 mm	12 mm	14 mm		10 mm	11 mm	12 mm	
Control	NI	NI	NI		NI	NI	NI	
Note: Standard: Ofloxacin (2 µg/ml); (NI): No Zone of Inhibition; Control: DMSO solvent								

Table-3: Antifungal activity of newly synthesized flavone derivatives (5a-d)

Compound code	Zone of inhibition in mm							
	Aspergillus niger				*Candida albicans*			
	Concentration of compounds (µg/ml)				Concentration of compounds (µg/ml)			
	100	250	500	Std.	100	250	500	Std.
5a	NI	NI	NI	15 mm	NI	NI	NI	14 mm
5b	NI	NI	NI		NI	11 mm	12 mm	
5c	NI	10 mm	11 mm		NI	10 mm	11 mm	
5d	NI	NI	NI		NI	11 mm	12 mm	
Control	NI	NI	NI		NI	NI	NI	
Note: Standard: Amphotericin (50 µg/ml); (NI): No Zone of Inhibition; Control: DMSO solvent								

According to the obtained results, compounds 5a, 5b and 5c showed zero zones of inhibition at all the tested concentrations and were found to be inactive against *E. coli* and *S. aureus* while compound 5d showed 10, 12, 14 mm and 10, 11, 12 mm zones of inhibition respectively at 100 µg/ml, 250 µg/ml and 500 µg/ml against *E. coli* and *S. aureus* organisms. Standard ofloxacin (2 µg/ml) showed 20 mm and 22 mm zones of inhibition respectively against bacteria *E. coli* and *S. aureus*. In case of antifungal sensitivity, compounds 5a, 5b and 5d showed no zones of inhibition at all the concentrations and were found to be inactive against *A. niger*, while compound 5c showed 10 and 11mm of zone at 250 µg/ml and 500 µg/ml concentrations respectively against *A. niger*. Standard amphotericin (50 µg/ml) showed 15 mm of zone against *A. niger*. As far as fungus *C. albicans* is concern, compound 5b, 5c, 5d were found to show 11, 12; 10, 11; and 11, 12 mm of zones of inhibition at 250 µg/ml and 500 µg/ml concentrations respectively whereas compound 5a was found to be inactive against *C. albicans* at all the tested concentrations when compared with std. amphotericin drug which showed 14 mm of zone against *C. albicans*.

Table-4: Antioxidant activity of newly synthesized flavone derivatives (5a-d)

Compd. code	% Scavenging of synthesized compounds (5a-d) and std. Ascorbic acid				
	10 µg/ml	20 µg/ml	30 µg/ml	40 µg/ml	50 µg/ml
5a	39.69	45.17	59.42	68.34	79.76
5b	19.51	23.46	24.78	30.33	38.56
5c	26.97	35.96	46.92	60.22	75.09
5d	21.05	35.96	36.84	59.70	71.00
Standard	80.26	91.22	95.61	96.27	97.80

Table-5: Anti-inflammatory activity of newly synthesized flavone derivatives (5a-d)

Compd. code	% Inhibition of synthesized compounds (5a-d) and std. Ibuprofen drug				
	10 µg/ml	20 µg/ml	30 µg/ml	40 µg/ml	50 µg/ml
5a	31.51	59.71	66.72	76.85	85.43
5b	51.65	52.81	54.30	59.95	67.76
5c	39.18	40.17	53.09	60.41	74.38
5d	47.67	52.81	66.39	73.11	81.67
Standard	87.36	88.90	90.23	91.74	93.10

The experimental data on antioxidant activities (Table-4) reveals that, compounds 5a, 5c and 5d showed good scavenging activity while compound 5b showed mild scavenging activity with reference to std. ascorbic acid. Also, one thing is noted that, as the concentration of test compounds increases, their percentage of scavenging also increases. In case of anti-inflammatory activities, we observed that, compounds 5a and 5d showed excellent inhibition to protein denaturation as compared to compound 5b and 5c which showed moderate to good inhibition to protein denaturation with comparison to std. NSAID ibuprofen drug.

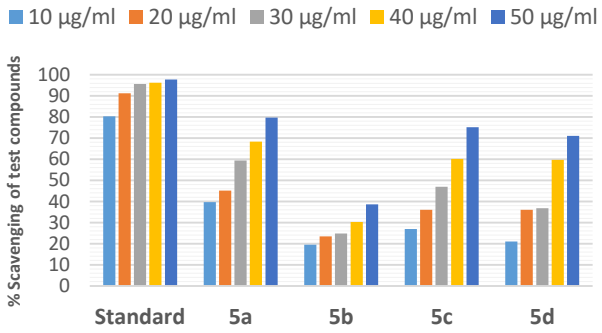


Figure-2: Graph showing percentage of scavenging of test compounds (5a-d)

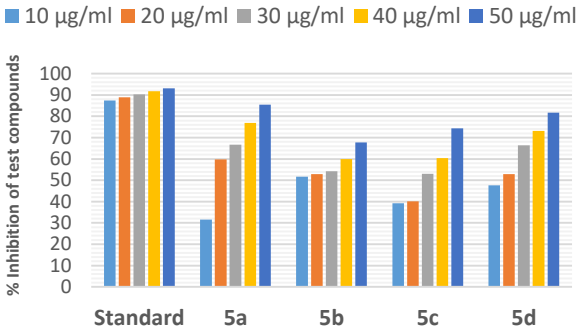


Figure-3: Graph showing percentage of inhibition of test compounds (5a-d)

CONCLUSION

In conclusion, a total four novel flavones viz. 2-(substituted phenyl)-6-chloro-7-methyl-4*H*-chromen-4-one (5a-d) were successfully synthesized by dehydrative cyclization of β-diketones bearing moiety of p-chloro-m-cresol and characterized by spectral studies. All the synthesized compounds were evaluated for their antimicrobial, antioxidant and anti-inflammatory potential *in vitro*. From the results, it was clear that, only the compound 5d was moderately active while compounds 5a, 5b and 5c were found to be inactive against *E. coli* and *S. aureus* as compared to std. antibiotic ofloxacin. Also, it was found that, only the compound 5c was moderately active against *A. niger* while compounds 5a, 5b, 5d do not shown inhibitory action and were found to inactive against *A. niger* when compared with std. amphotericin drug. As far as *C. albicans* is concern, instead of compound 5a, the compounds 5b, 5c, and 5d were found to show moderate to good inhibitory action to growth response of fungus *C. albicans*. The results on antioxidant and anti-inflammatory activities reveals that, among the newer derivatives, compounds 5a, 5c, 5d showed a promising antioxidant activity as well as all the compounds showed notable and excellent anti-inflammatory activities with comparison to std. reference drugs. It is conceivable that these newly synthesized flavones showing *in vitro* scavenging and protein denaturation activity can be further modified to achieve marketable antioxidant and NSAID agents.

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59

Design, Synthesis, Spectral Characterisation and Antibacterial Screening of Some Novel 4- Substitutedimino-1,3,5-Dithiazine Along With Pyrimidine Nucleus

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ABSTRACT

In recent times in the laboratory, synthesis of 2-(2-Phenylimino-4- substitutedimino-1,3,5-dithiazino) aminopyrimidine **(IIIa-e)** were synthesized by refluxing 2-(5-phenyl-,4-dithiobiureto) pyrimidine **(I)** with alkyl/ arylisocyanodichlorides **(IIa-e)** in acetone-ethanol medium in 1:1 molar proportion. The structures of all the synthesized compounds were acceptable on the basis of chemical characteristics, elemental analysis, spectral studies and their antibacterial screening against the gram positive and gram negative bacteria such as *S. typhi, E. coli, S. aureus, A. Aerogenes, B. Subtilis* and *B. Megatherium.etc*.

INTRODUCTION

Heterocycles containing organic molecules are more fascinating, because they are convenient in a variety of applications, a multitude of uses are included by the heterocycles' size and heteroatom diversity. These compound nitrogen, oxygen and sulphur are composed of six member[1-5], five member[6-7] fused heterocycles with aromatic rings. Particularly noteworthy are the numerous biological and industrial uses for heterocycles that combine sulphur and nitrogen in one ring. Six member two sulphur and one nitrogen atom prepare 1,3,5-dithiazine. It is one of the six member heterocycles that functions as a strong medication in the sectors of medicine, agriculture, and industry[9-8].

Tayade[10], Pathe[11] and Mur[12] Synthesized numerous heterocycles containing 1,3,5-dithiazines as main nucleus. Each 1,3,5-dithiazino moiety has different applications according to the substituent attached to the basic nucleus of the 1,3,5-

ithiazine. It has been also observed during literature study that, 1,3,5-dithiazino nucleus and its derivatives possesses biological and medicinal effective properties[13-14]. Substituted isocyanodichlorides were used by researchers to synthesise 1,3,5- dithiazines in the laboratory. This 1,3,5-dithiazine synthesis technique is quicker, less complicated, less expensive and requires less time.

MATERIAL AND METHOD

Material

All the chemical used were of loba chemie (AR grade).

Method

In the present experiment for the synthesis of different substituted 1,3,5-dithiazino

aminopyrimidine is conventional refluxing under electronic water bath for different hours for different experiment**.**

EXPERIMENTAL

All the chemicals used for the synthesis were purified. After refluxing the purity of the compounds were checked by TLC (aluminium TLC) with thin layer thickness of 200 um. The melting points of all synthesize compounds will be recorded using hot paraffin bath. The carbon and hydrogen analysis were carried out on Carlo-Ebra-1106 analyser Nitrogen estimation were carried out with colmon-N-analyzer-29. IR spectra were recorded with Bruker spectrometer in the range 4000-400 cm-1. PMR spectra were recorded on VARIAN 400 MHz spectrometer with TMS as internal standard using $CDCL_3$ and DMSO Solvent.

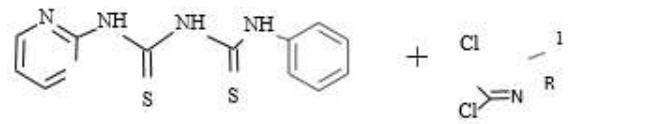
GENERAL PROCEDURE

A reaction of 2-(5-phenyl-2,4-dithiobiureto)pyrimidine **(I)** and substitutedisocyanodichloride **(IIa-e)** in 1:1 molar ratio refluxed on water bath in acetone-ethanol medium for 2 hours. The evolution of the hydrochloride gas was clearly observed during refluxtion. After distillation of excess solvent orange product isolated which on basification with dilute ammonium hydroxide orange crystalline products obtained.

Similar, procedure was adopted for the synthesis of all the derivatives in the series.

The tentative reaction for the formation of product is depicted below,

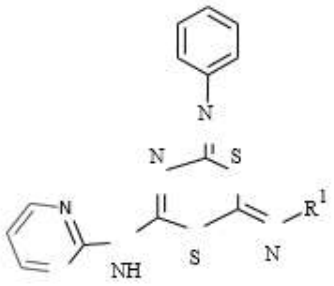
Reaction



2-(5-Phenyl-2,4-dithiobiureto)pyrimidine **(I)** Substitutedisocyanodichloride

(IIa-e)





2-(2-Phenylimino-4-substitutedimino-1,3,5-dithiazino)aminopyrimidine

(IIIa-e)

Similarly, 2-(5-phenyl-2,4-dithiobiureto)pyrimidine **(I)** were react with

phenylisocyanochloride **(IIa),** ethylisocyanodichloride **(IIb),** tertbutylisocyanodichloride **(IIc**), P-tolylisocyanodichloride **(IId**) and 4-chlorophenhylisocyanodichloride (**IIe)** by the above mentioned method to isolate 2-[2,4-di(phenylimino)-1,3,5-dithiazino] aminopyrimidine **(IIIa)**, 2- (2-phenylimino-4-ethylimino-1,3,5-dithiazino) aminopyrimidine**(IIIb)**, 2-(2-phenylimino-4- *tert*-butylimino-1,3,5-dithiazino) aminopyrimidine **(IIIc)**, 2-[2-phenylimino-4-(4- methylphenylimino)-1,3,5-dithiazino]aminopyrimidine **(IIId)** and 2-[2-phenylimin-4-(4- chlorophenylimino)-1,3,5-dithiazino]aminopyrimidine **(IIIe).**

RESULT AND DISCUSSION

Spectral characterization results for all the synthesized compounds are given below

Spectral Characterization

1. 2-(2,4-diphenylimino-1,3,5-dithiazino)aminopyrimidine (IIIa)

Colour-Yellow solid, **Molecular formula**- $C_{15}H_{14}N_6S_2$, **Yield** 85%, **M.P**. 162^{0}C, **% Composition found (calculated)** C-52.90 , H-4.83 , N-25.20, S-23.21 , **FTIR (Kbr) vcm**- 3245.22 N-H stretching, 3051.47 (C-H Ar Stretching), 3187.38 (N-H Amido), 1950.37 (C-H Ar Bending,), 1185.99 (C=S Stretching), 670.04(=C-H bending); **1H NMR (400MHz $CDCL_3$ δ ppm)**, 8.4ppm (2H, double, CH) of pyrimidine, 7.2ppm (2H, CH, doublet) of pyrimidine, 7.2 ppm (2H, , doublet CH) of phenyl, 3.4 ppm (1H, singlet NH), 4.6 ppm 1H singlet, 7.39 1H triplet CH benzene, 1H triplet CH benzene

2.2 ppm 2H quartet, 2.3 ppm 3H triplet **Mass** m/z 390.30

2. 2-(2-phenylimino-4-ethylimino-1,3,5-dithiazino)aminopyrimidine (IIIb)

Colour-Yellow solid, **Molecular formula**- $C_{15}H_{14}N_6S_2$, **Yield** 86%, **M.P**. 170^{0}C, **% Composition found (calculated)** C-52.90 , H-4.83 , N-25.20, S-23.21 , **FTIR (Kbr) vcm**- 3245.22 N-H stretching, 3051.47 (C-H Ar Stretching), 3187.38 (N-H Amido), 1950.37 (C-H Ar Bending,), 1185.99 (C=S Stretching), 670.04(=C-H bending); **1H NMR (400MHz $CDCL_3$ δ ppm)**, 8.4ppm (2H, double, CH) of pyrimidine, 7.2ppm (2H, CH, doublet), 7.2 ppm (2H, , doublet CH) of phenyl, 3.4 ppm (1H, singlet NH),

4.6 ppm 1H singlet, 7.39 1H triplet CH benzene, 1H triplet CH benzene 2.2 ppm 2H quartet, 2.3 ppm 3H triplet **Mass** m/z 342.30

3. 2-(2-phenylimino-4-tertbutylimino-1,3,5-dithiazino)aminopyrimidine (IIIc)

Colour-Yellow solid, **Molecular formula**- $C_{17}H_{18}N_6S_2$, **Yield** 90%, **M.P**. 158^{0}C, **% Composition found (calculated)** C-55.90 , H-4.83 , N-23.20, S-17.21 , **FTIR (Kbr) vcm**- 3245.22 N-H stretching, 3045.47 (C-H Ar Stretching), 3140.38 (N-H Amido), 1995.37 (C-H Ar Bending,), 1164.99 (C=S Stretching), 710.04(=C-H bending); **1H NMR (400MHz $CDCL_3$ δ ppm)**, 8.2ppm (2H, double, CH), 7.2ppm (2H, CH, doublet), 7.1ppm (2H, , doublet CH), 3.5 ppm (1H, singlet NH), 4.5 ppm 1H singlet, 7.40 1H triplet CH benzene, 2.4 9H singlet **Mass** m/z 370.50

4. 2-(2-phenylimino-4-tolylimino-1,3,5-dithiazino)aminopyrimidine (IIId)

Colour-Yellow solid, **Molecular formula**- $C_{20}H_{16}N_6S_2$, **Yield** 82%, **M.P**. 167^{0}C, **% Composition found (calculated)** C-55.90 , H-4.83 , N-23.20, S-15.21 , **FTIR (Kbr) vcm**- 3200.22 N-H stretching, 2901.47 (C-H Ar Stretching), 316038 (N-H Amido), 1960.37 (C-H Ar Bending,), 1167.99 (C=S Stretching), 745.04(=C-H bending); **1H NMR (400MHz $CDCL_3$ δ ppm)**, 8.2 ppm (2H, double, CH) of pyrimidine, 7.3ppm (2H, CH, doublet), 7.2 ppm (2H, , doublet CH), 3.5 ppm (1H, singlet NH), 4.7 ppm 1H singlet, 7.39 1H triplet CH benzene, 3.4 ppm 3H singlet. **Mass** m/z 404.60

5. 2-(2-phenylimino-4-p-chlorophenylimino-1,3,5-dithiazino)aminopyrimidine (IIIe)

Colour-Yellow solid, **Molecular formula**- $C_{19}H_{13}N_6S_2$, **Yield** 80%, **M.P**. 145^0C, **% Composition found (calculated)** C-53.90 , H-3.83 , N-20.20, S-15.21Cl-8.45 , **FTIR (Kbr) vcm**- 3263.22 N-H stretching, 3051.47 (C-H Ar Stretching), 3216.38 (N-H Amido), 1966.37 (C-H Ar Bending,), 1165.99 (C=S Stretching), 720.04(=C-H bending); **1H NMR (400MHz CDCL$_3$ δ ppm)**, 8.4 ppm (2H, double, CH) of pyrimidine, 7.03ppm (2H, CH, doublet), 7.4 ppm (2H, , doublet CH), 3.5 ppm (1H, singlet NH), 4.6 ppm 1H singlet, 7.39 1H triplet CH benzene, **Mass** m/z 424.80.

CONCLUSION

In the present work is cheaper and less time consuming method for synthesis of organic compound (IIIa-e). In all the synthesized compounds give the maximum yield of product (III a-e). A variety of pyrimidine based 1,3,5-dithiazine derivative can be synthesized for their antimicrobial activities adopting the method.

PHARMACOLOGICAL STUDIES

Antimicrobial activity

All the synthesized compounds **(III-a)** to **(III-e)** were screened for antibacterial activity against *S. typhi*, *E. coli*, *S. aureus*, *A. Aerogenes*, *B. Subtilis* and *B. Megatherium.* by disc diffusion method was performed using mueller hinton agar as well as nutrient agar medium. Each and every compound was tested at conc. 50 µg/ml in ethanol. The zone of inhibition of all the synthesized compounds were measured after 24 hour incubation at 37 ^{0}C. Standard drug used for comparison the activity was Ciprofloxacin.

Table 1: Synthesized compound **IIIa-e** activity against Gram +ve and Gram -ve bacteria

Table No. 1.1 - Antibacterial activity of synthesized compound against bacteria (Zone of inhibition in mm) (after 24 hrs at 37 ºC temp)

SR No.	Compd.	Gram positive			Gram negative		
		S. aureus	***B. subtilis***	***B. megatherium***	***S. typhi***	***E. coli***	***A. aerogenes***
1	**SBS-IIIa**	18	12	16	14	18	11
2	**SBS-IIIb**	11	12	14	14	11	12
3	**SBS-IIIc**	11	11	12	11	11	11
4	**SBS-IIId**	10	12	12	12	11	11
5	**SBS-IIIe**	14	12	14	12	16	12
6	**Std Ciprofloxacin**	18	16	20	18	20	14

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60

Colorimetric Phytochemical Analysis of Tinospora Cordifolia and FTIR Study of Its Medicinal Sample Giloy Ghanvati

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ABSTRACT

Tinospora cordifolia (common names gurjo, heart-leaved moonseed, guduchi or giloy) is a herbaceous vine of the family Menispermaceae indigenous to tropical regions of the Indian subcontinent. It has been used in Ayurveda to treat various disorders. Tinospora cordifolia contains diverse phytochemicals, including alkaloids, phytosterols, glycosides, tinosporide, and other mixed chemical compounds. During the 2020-22 COVID-19 outbreak in India, the Ministry of AYUSH recommended use of Giloy as a home remedy for immune support. Giloy extract was assessed for its phytochemical and antibacterial properties, to find out the bioactive components responsible for such activity.

In Ayurveda, it is said to be the best rejuvenating herb. Acute toxicity studies of aqueous extract of Guduchi reports that it does not produce any toxic effect. The medicinal herb has to be used in an appropriate dose as prescribed by a qualified physician to get medicinal effects. With the wide range of actions and abundant components, Guduchi is a real treasure among herbal drug source. Medicinal applications of Guduchi in countering various disorders and it's use as anti-oxidant, anti-hyperglycemic, anti-hyperlipidemic, hepatoprotective, cardiovascular protective, neuroprotective, osteoprotective, radioprotective, anti-anxiety, adaptogenic, analgesic, anti-inflammatory, anti-pyretic, anti-diarrheal, anti-ulcer, anti-microbial, and anti-cancer have been well established.

Present study deals with Colorimetric phytochemical analysis of Tinospora Cordifolia (Giloy leaf extract) and FTIR study of its medicinal sample Giloy Ghanvati. Colorimetric phytochemical analysis of Tinospora Cordifolia (Giloy leaf extract) involves preparation of standard Giloy Ghanvati solution, Ferric Chloride solution and Giloy leaf Solution. Different systems were prepared. Absorbance of standard Giloy solution was taken at different wavelength. And λmax was calculated. Which was 420 nm. Absorbance of standard Giloy solution of different concentrations were taken at 420 nm and Calibration plot was prepared. Then absorbance of Giloy leaf solutions were taken at 420 nm and concentration of Giloy in Giloy leaf was calculated from calibration plot. Tinospora cordifolia which contains diverse phytochemicals, including alkaloids, phytosterols, glycosides, tinosporide, and other mixed chemical compounds reduces ferric ions and production of violet coloration by addition of ferric chloride to dilute solution of Giloy takes place and the concentration of Giloy was investigated colorimetrically. The method is simple, rapid and precise. Interpretation of FTIR Spectra of Giloy Ghanvati medicinal sample shows presence of various functional groups such as O-H stretching - Alcohol, Carboxylic acid, O-H bending - Alcohol, N-H stretching - Amine salt, C=C stretching - α, β- unsaturated ketone and C=O stretching - Conjugated acid.

Keywords: Tinospora cordifolia, Giloy, Giloy ghanvati, Colorimetric Phytochemical Analysis, FTIR study

INTRODUCTION

Giloy

Tinospora cordifolia (common names gurjo, heart-leaved moonseed, guduchi or giloy) is a herbaceous vine of the family Menispermaceae indigenous to tropical regions of the Indian subcontinent. It has been used in Ayurveda to treat various disorders, but in spite of clinical investigation, the effectiveness of such treatments remains uncertain. [1] Reddish fruits of Tinospora cordifolia is a large, deciduous, extensively-spreading, climbing vine with several elongated twining branches.

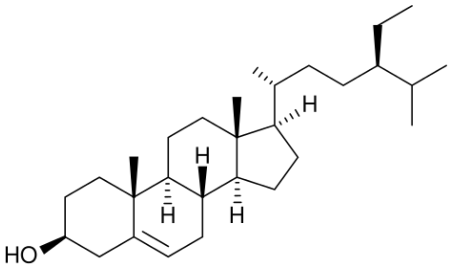


Leaves of Tinospora cordifolia

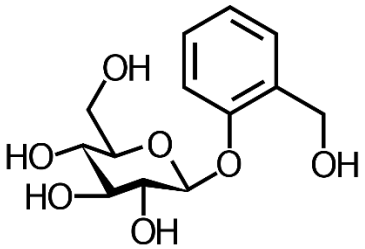


Fruits of Tinospora cordifolia

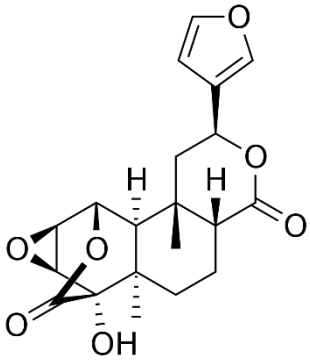
Endophytic fungi colonize the living, internal tissues of their host without causing any harmful effects. A recent study has shown that 29 endophytes belonging to different taxa were present in the samples collected from Tinospora cordifolia.[2] Extracts of the endophytic fungus Nigrospora sphaerica obtained from T. cordifolia were found to have insecticidal properties against the Oriental leafworm moth (Spodoptera litura), a polyphagous pest.[3] Tinospora cordifolia contains diverse phytochemicals, including alkaloids (Alkaloids are a class of basic, naturally occurring organic compounds that contain at least one nitrogen atom), phytosterols, glycosides, tinosporide,[4] and other mixed chemical compounds. Although used in Ayurveda over centuries in the belief that Tinospora has medicinal properties.[5]



Phytosterols



Glycosides

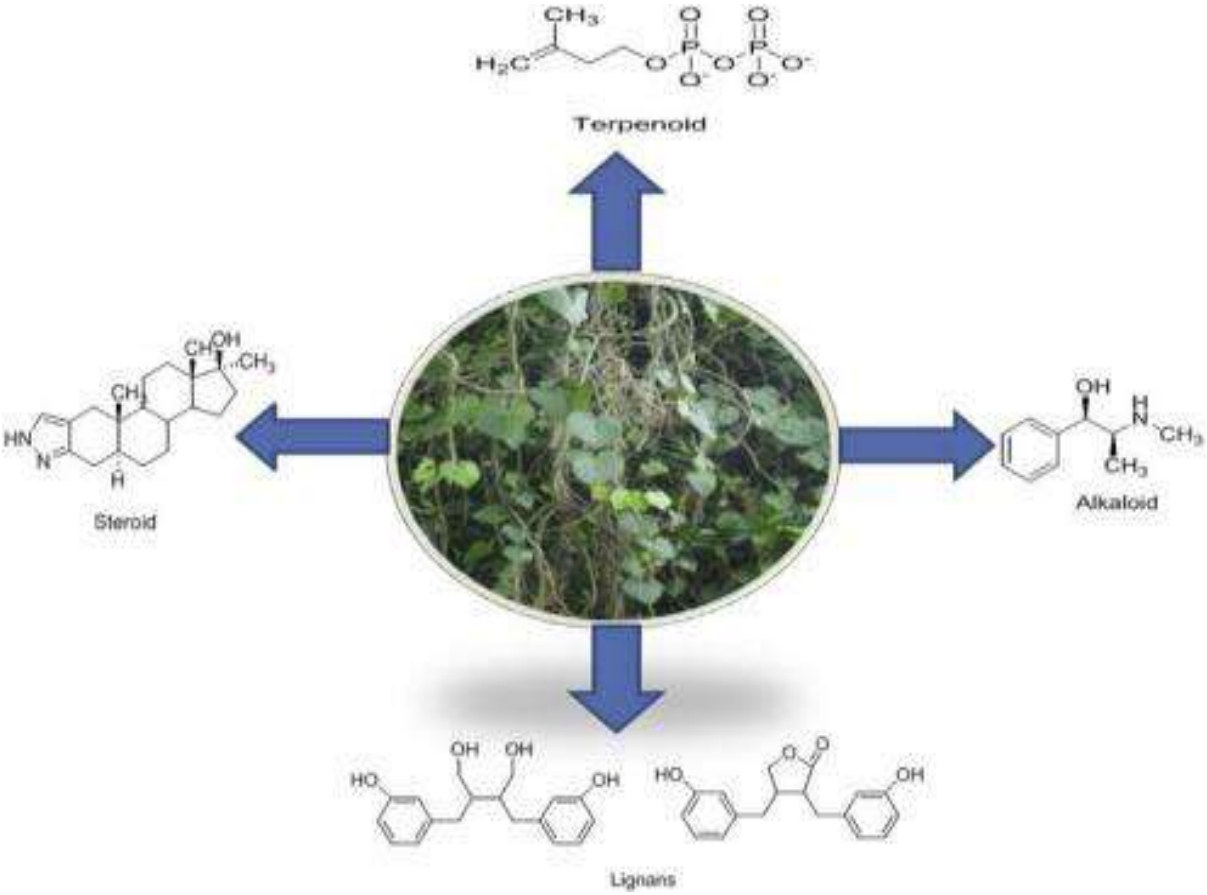


Tinosporide

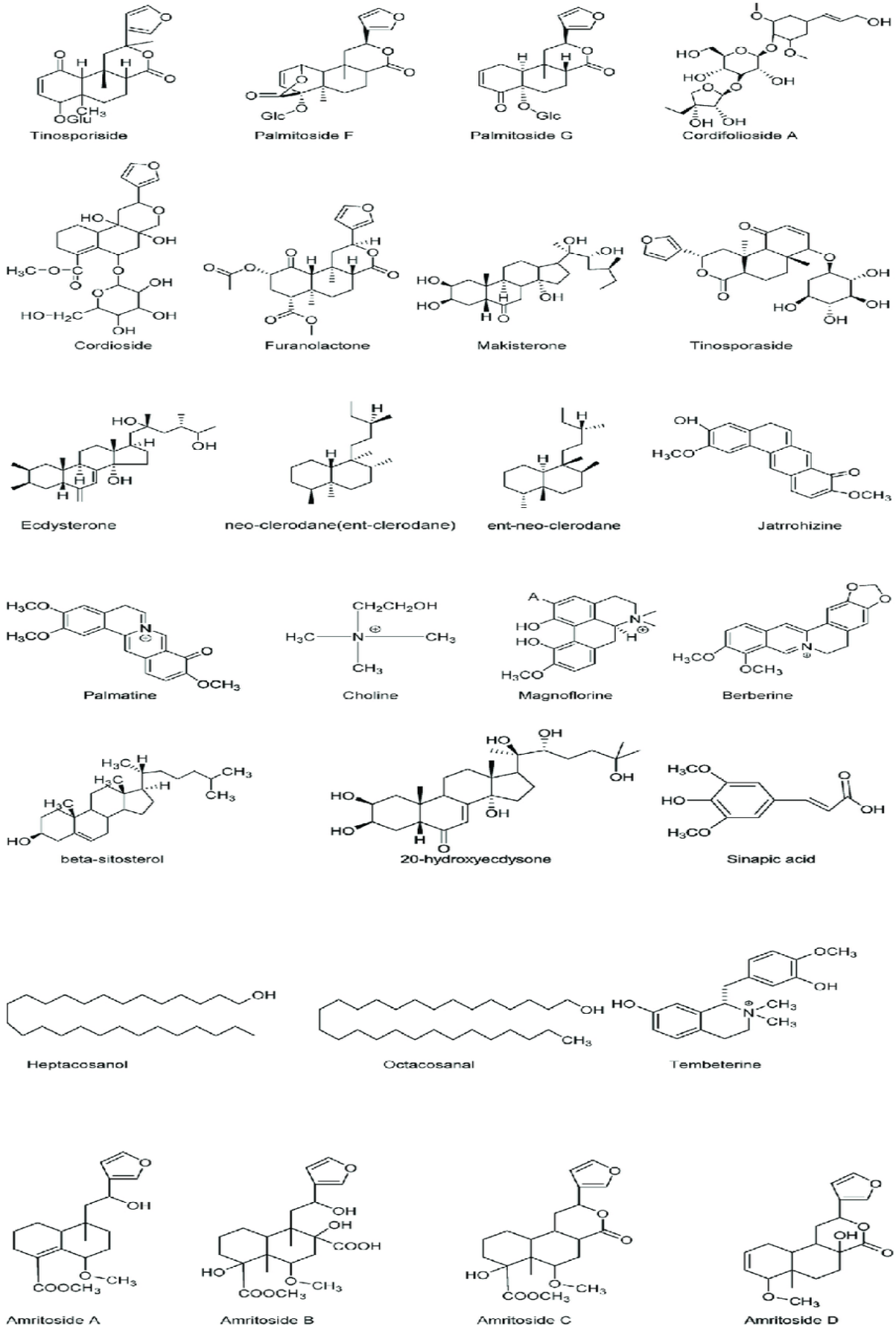
During the 2020-22 COVID-19 outbreak in India, the Ministry of AYUSH recommended use of T. cordifolia (Giloy) as a home remedy for immune support, [6] but such a practice appeared

to be associated with hepatitis cases among six people in Mumbai who used boiled or capsule preparations of the plant. [6-9]

Tinospora cordifolia is a popular medicinal plant which is used in several traditional medicines to cure various diseases. The common names are Amrita and Guduchi and belong to the family of Menispermaceae. It is considered an essential herbal plant of Indian system of medicine (ISM) and has been used in the treatment offever, urinary problem, dysentery, skin diseases leprosy, diabetes, and many more diseases. The plant reported containing chemical compound including Alkaloids, Terpenoids, Lignans, Steroids and others that establish the phytochemistry and pharmacological activity of Tinospora cordifolia. The study highlights the pharma-cological importance viz antioxidant activity, antimicrobial activity, antibacterial activity, antifungal activity, anti-diabetic activity, antistress activity, hypolipidaemic effect, hepatic disorder, anticancer anti HIV potential, antiosteoporotic effects, antitoxic effects, wound healing, anticomplementary activity, and immunomodulating activity, systemic infection and Parkinsons disease. [10]



Major constituent of Tinospora cordifolia: terpenoid, alkaloid, lignans, steroids. [10]



Structure of the chemical constituent of T. cordifolia. [10]

Some of the essential constituents of T. cordifolia.
Terpenoids Tinosporide, Furanolactone diterpene, Furanolactone clerodane diterpene, furanoid diterpene, Tinosporaside, ecdysterone makisterone and several glucosides isolated as poly acetate, phenylpropene disaccharides cordifolioside A, B and C, cordifoliside D and E, Tinocordioside, cordioside, palmatosides C and F, Sesquiterpene glucoside tinocordifolioside, Sesquiterpene tinocordifolin. [11-21]
Alkaloids Tinosporine, (S), Magnoflorine, (S), Berberine, (S), Choline, (S), Jatrorrhizine, (S), 1,2-Substituted pyrrolidine(S), Alkaloids, viz. jatrorrhizine, palmatine, beberine, tembeterine, choline. [12-26]
Lignans 3 (a, 4-dihydroxy-3-methoxybenzyl)-4-(4- hydroxy-3-methoxybenzyl), (S) [27]
Steroids Giloinsterol, (S), ß-Sitosterol, (S), 20aHydroxy ecdysone, (S). [28-31]
Others Giloin, Tinosporan acetate, Tinosporal acetate, Tinosporidine, Heptacosanol, Octacosanol, sinapic acid, Tinosponone, two phytoecdysones, an immunologically active arabinogalactan. [32-36]

The study planned to prepare antibacterial finish for grey cotton fabric using Giloy stem extract for healthcare applications. The selected grey cotton fabric was pretreated prior to application of the extract. For the extraction of the herb, maceration process was employed and the solution prepared was further subjected to soxhlet extraction to congeal the extract. Giloy extract was assessed for its phytochemical and antibacterial properties, to find out the bioactive components responsible for such activity. [37]

Certain sections of the media have falsely linked again Giloy/Guduchi to liver damage. The Ministry of Ayush reiterates that Giloy/Gudduchi (Tinospora cordifolia) is safe and as per available data, Guduchi does not produce any toxic effect. In Ayurveda, it is said to be the best rejuvenating herb. Acute toxicity studies of aqueous extract of Guduchi reports that it does not produce any toxic effect. However, the safety of a drug depends on how it is being used. Dosage is one of the important factors that determine the safety of a particular drug. In a study, lower concentration of Guduchi powder is found to increase the life span of fruit flies (Drosophila Melanogaster). At the same time, higher concentration progressively reduced the life span of flies. This clearly indicates that an optimum dosage should be maintained in order to get the desired effects. This infers that the medicinal herb has to be used in an appropriate dose as prescribed by a qualified physician to get medicinal effects. With the wide range of actions and abundant components, Guduchi is a real treasure among herbal drug source. Medicinal applications of Guduchi in countering various disorders and it's use as anti-oxidant, anti-hyperglycemic, anti-hyperlipidemic, hepatoprotective, cardiovascular protective, neuroprotective, osteoprotective, radioprotective, anti-anxiety, adaptogenic, analgesic, anti-inflammatory, anti-pyretic, anti-diarrheal, anti-ulcer, anti-microbial, and anti-cancer have been well established.

A special focus has been made on its health benefits in treating various metabolic disorders and its potential as an immune booster. It is used as a major component of therapeutics for ameliorating metabolic, endocrinal, and several other ailments, aiding in the betterment of human life expectancy. It is a popularly known herb for its immense therapeutic applications in traditional systems of medicine and has been used in the management of COVID-19. Considering the overall health benefits, the herb cannot be claimed to be toxic.[38]

During the ongoing COVID-19 pandemic *Tinospora cordifolia* also known as Giloy gained immense popularity and use due to its immunity-boosting function and anti-viral properties. *T. cordifolia* is among the most important medicinal plants that has numerous therapeutic

applications in health due to the production of a diverse array of secondary metabolites. Therefore, to gain genomic insights into the medicinal properties of *T. cordifolia*, the first genome sequencing was carried out using 10x Genomics linked read technology and the draft genome assembly comprised of 1.01 Gbp. This is also the first genome sequenced from the plant family Menispermaceae. The deep sequencing of transcriptome from the leaf tissue was also performed followed by transcriptomic analysis to gain insights into the gene expression and functions. Further, the phylogenetic position of *T. cordifolia* was also determined through the construction of a genome-wide phylogenetic tree using 35 other dicot species and one monocot species as an outgroup species.[39]

Plants produce a diverse range of bioactive molecules, making them a rich source of different types of medicines. A regular and widespread use of herbs throughout the world has increased serious concern over their quality, safety and efficacy. Thus, a proper scientific evidence or assessment has become the criteria for acceptance of herbal health claims. The anti-oxidant effects of leaves of Tinospora cordifolia has been examined. [40]

The phytochemical analysis of the plants is very important commercially and has great interest in pharmaceutical companies for the production of the new drugs for curing of various diseases. Phytochemicals have two categories i.e., primary and secondary constituents. Primary constituents have chlorophyll, proteins sugar and amino acids. Secondary constituents contain terpenoids and alkaloids. Medicinal plants have antifungal, antibacterial and anti-inflammation activities. Study involves the qualitative phytochemical analysis of two different medicinal plants: Tinospora cordifolia and Withania somnifera. Data indicates the presence of flavonoids, alkaloids, proteins, phenolic compounds, cardiac glycosides and tannins. [41]

Tinospora cordifolia is known as Giloe and Guduchi, with significant importance in the traditional medicinal systems. It is dioeciously plant. It is mostly used in Ayurved system. It is also known as a 'Rasayans' of medicinal system, which develops immune system of the body and protect against infection. Study is carried out to analyse the phytochemical compounds in leaves and stem extracts of T. cordifolia by using phytochemical screening tests and estimate total flavonoid content (TFC) by using aluminium chloride method in the sample extracts. The leaf and stem extracts of T. cordifolia expressed the presence of several phytochemicals viz., flavonoids, amino acids, diterpines, protein, saponins and carbohydrates. The investigation further proposed that the phytochemicals present in stems and leaves of T. cordifolia, which can be use as natural antioxidants in medicinal drugs. [42]

The traditional system of medicine in Sri Lanka has shown much better improvement, has fewer side effects, and is less expensive than modern synthetic drugs in the treatment of many diseases. The objective of the was to comparatively evaluate the qualitative and quantitative analysis of phytochemical constituents of leaves of Murraya koenigii (L.) Spreng., Tinospora cordifolia (Wild) Hook.f., Enicostemma axillare (Lam) A. Raynal, and Gymnema sylvestre R. Br. were collected from Jaffna District. [43]

Patanjali Giloy Ghanvati

Giloy ghanvati is used as a treatment for general fever and immunity. Useful in generalized debility, fever, skin & urinary disorders. It is also beneficial in general weakness, fever, dengue, chicken guinea. It helps build strength and enhance energy, boosts immunity naturally, offers protection against numerous diseases, alleviates weakness and fatigue. [44]

Patanjali Ayurveda Giloy Ghanvati is an ayurvedic supplement that helps boost immunity and protect from various infections. Its key ingredient is Giloy. It helps build strength and stamina to improve energy levels. The tablets aid in post-illness recovery and manage fever, cough, and cold. Giloy, an active ingredient in the tablet, has an antipyretic activity that helps to reduce fever and recover quickly after an infection or illness. It is known to alleviate the symptoms of the common cold, low immunity, general weakness, and fatigue. This ayurvedic tablet is also known to increase platelet count and reduce dengue fever. It also aids in toxin removal, promoting better skin and skin regeneration by increasing collagen production. It can be used for general weakness and the common cold**,** Aids in relieving constipation with mucus in the stool**,** helps to manage cholesterol levels and keep your heart healthy**,** it is known to lower your risk of recurrent infections, boosts your immune system and prevents immune-deficiency disorders**,** acts as supportive therapy for individuals with autoimmune disorders, it improves your appetite and aids in overall growth**,** plays a key role in the treatment of skin conditions**,** helps deal with urinary problems, including urinary tract infections. [45]

The current severe acute respiratory syndrome disease caused by Coronavirus-2 (SARS-CoV-2) has been a serious strain on the healthcare infrastructure mainly due to the lack of a reliable treatment option. Alternate therapies aimed at symptomatic relief are currently prescribed along with artificial ventilation to relieve distress. Traditional medicine in the form of Ayurveda has been used since ancient times as a holistic treatment option rather than targeted therapy. The practice of Ayurveda has several potent herbal alternatives for chronic cough, inflammation, and respiratory distress which are often seen in the SARS-CoV-2 infection. The aqueous extracts of *Tinospora cordifolia* (willd.) Hook. f. and Thomson in the form of Giloy Ghanvati, as a means of treatment to the SARS-CoV-2 spike-protein induced disease phenotype in a humanized zebrafish model is used. The resultant changes in the disease phenotype were comparable to the group that were given the reference compound, Dexamethasone. These findings correlated well with various phyto-compounds detected in the Giloy Ghanvati and their reported roles in the viral disease phenotype amelioration.[46]

Present study deals with Colorimetric phytochemical analysis of Tinospora Cordifolia (Giloy leaf extract) and FTIR study of its medicinal sample Giloy Ghanvati. Colorimetric phytochemical analysis of Tinospora Cordifolia (Giloy leaf extract) involves preparation of standard Giloy Ghanvati solution, Ferric Chloride solution and Giloy leaf Solution. Different systems were prepared. Absorbance of standard Giloy solution was taken at different wavelength. And λmax was calculated. Which was 420 nm. Absorbance of standard Giloy solution of different concentrations were taken at 420 nm and Calibration plot was prepared. Then absorbance of Giloy leaf solutions were taken at 420 nm and concentration of Giloy in Giloy leaf was calculated from calibration plot. Tinospora cordifolia which contains diverse phytochemicals, including alkaloids, phytosterols, glycosides, tinosporide, and other mixed chemical compounds reduces ferric ions and production of violet coloration by addition of ferric chloride to dilute solution of Giloy takes place and the concentration of Giloy was investigated colorimetrically. The method is simple, rapid and precise. Interpretation of FTIR Spectra of Giloy Ghanvati medicinal sample shows presence of various functional groups such as O-H stretching - Alcohol, Carboxylic acid, O-H bending - Alcohol, N-H stretching - Amine salt, C=C stretching - α, β- unsaturated ketone and C=O stretching - Conjugated acid.

METHODOLOGY

1. Colorimetric phytochemical analysis of Tinospora Cordifolia (Giloy)

Colorimetric phytochemical analysis of Tinospora Cordifolia (Giloy leaf extract) involves preparation of standard Giloy Ghanvati solution, Ferric Chloride solution and Giloy leaf Solution. Different systems were prepared. Absorbance of standard Giloy solution was taken at different wavelength. And λmax was calculated. Which was 420 nm. Absorbance of standard Giloy solution of different concentrations were taken at 420 nm and Calibration plot was prepared. Then absorbance of Giloy leaf solutions were taken at 420 nm and concentration of Giloy in Giloy leaf was calculated from calibration plot. Tinospora cordifolia which contains diverse phytochemicals, including alkaloids, phytosterols, glycosides, tinosporide, and other mixed chemical compounds reduces ferric ions and production of violet coloration by addition of ferric chloride to dilute solution of Giloy takes place and the concentration of Giloy was investigated colorimetrically. The method is simple, rapid and precise.

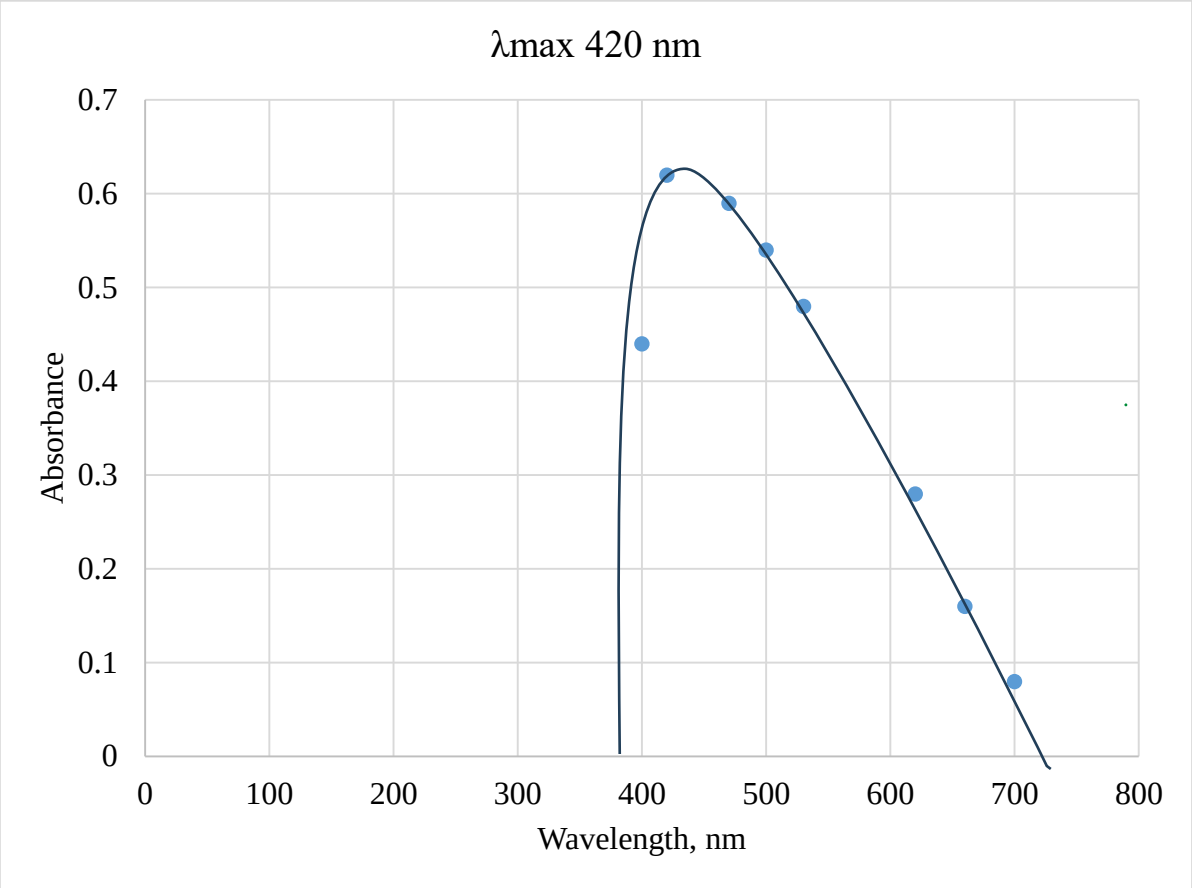
Preparation of Standard Giloy Ghanvati solution: Weight of 1 tablet of Giloy Ghanvati was taken and crushed it then 0.1 g powder was dissolved in 100 ml distilled water.
Preparation of Ferric Chloride solution: 1 g Ferric chloride was dissolved in 20 ml distilled water.
Preparation of Giloy Leaf Solution: 2 Giloy leaf was crushed with the help of distilled water, transferred completely in 100 ml volumetric flask and volume was made up to 100 ml with the help of distilled water.

Following systems were prepared

System No.	Standard Giloy Ghanwati Solution, ml	Giloy Leaf Solution	Ferric Chloride solution, ml	Distilled water
1	1	-	1	8
2	2	-	1	7
3	3	-	1	6
4	4	-	1	5
5	5	-	1	4
6	6	-	1	3
7	-	1	1	8
8	-	2	1	7
9	-	3	1	6
10	-	4	1	5
11	-	5	1	4
12	-	6	1	3

Absorbance of system No 1 taken at different wave length using water as blank. λmax was noted which is 420 nm. Absorbance of system 1 to 6 was taken at λmax 420 nm. Then absorbance of system 7 to 12 was taken at 420 nm wavelength. Calibration plot was prepared between Concentration of Giloy and Absorbance. And from this calibration plot concentration of Giloy from Giloy Leaf sample was calculated.

Wave length, nm	Absorbance of System No. 1	Wave length, nm	Absorbance of System No. 1
400	0.44	530	0.48
420	0.62	620	0.28
470	0.59	660	0.16
500	0.54	700	0.08

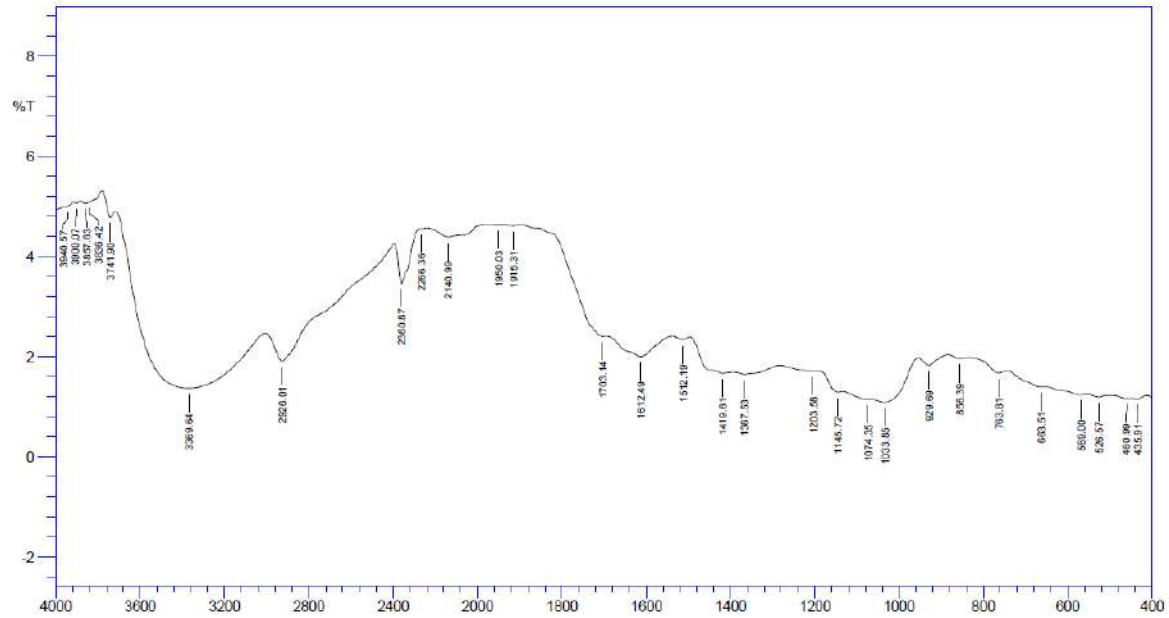


System No.	Absorbance at λmax 420 nm	System No.	Absorbance at λmax 420 nm
1	0.72	7	0.68
2	0.77	8	0.88
3	0.79	9	1.04
4	0.81	10	1.13
5	0.84	11	1.24
6	0.86	12	1.27

2. FTIR study of Giloy Ghanvati medicinal sample

FTIR can be routinely used to identify the functional groups and identification/quality control of raw material / finished products. Spectrum RX-I offers fast throughput and rapid access to reliable and dependable IR results. High signal to noise ratio makes FTIR more useful for difficult samples. It has resolution of 1 cm1 and scan range of 4000 cm^{-1} to 250 cm^{-1}. In the normal mode around 10 mg sample is required in the form of fine powder. The sample can be analyzed in the form of liquid, solid and thin films also.

FTIR spectra of Giloy Ghanvati medicinal sample is obtained at room temperature by using an FTIR Spectrophotometer – Perkin Elmer – Spectrum RX-IFTIR. The spectra is collected in a range from 400 to 4000 cm^{-1}.



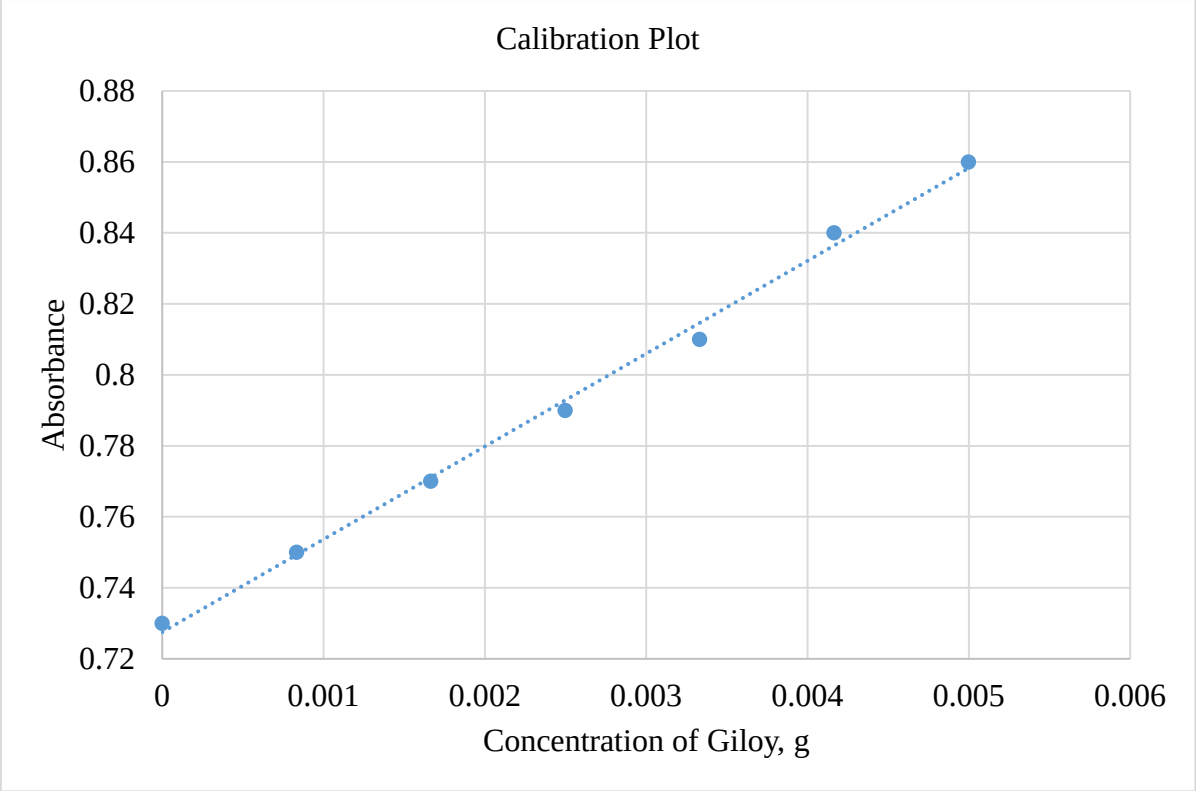
FTIR spectra of Giloy Ghanvati medicinal sample

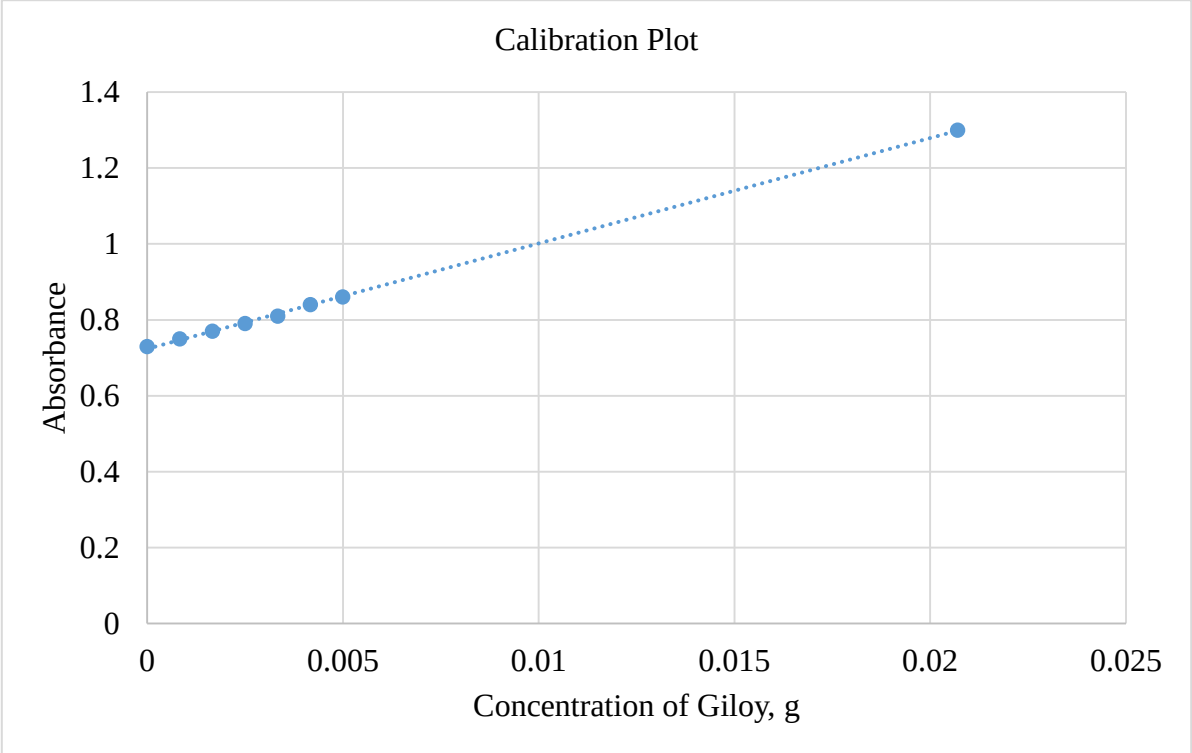
RESULTS AND DISCUSSION

1. Colorimetric phytochemical analysis of Tinospora Cordifolia (Giloy)

1 Tablet of Giloy Ghanvati contains 0.5 g Giloy (Quoted value).
Weight of 1 tablet of Giloy Ghanvati was 0.6 g. Hence 0.6 g tablet contains 0.5 g Giloy
0.1 g tablet powder will contains 0.1 x 0.5 / 0.6 = 0.0833 g Giloy.

System No	Volume of standard Giloy Ghanvati solution taken, ml	Weight of Giloy, g	Absorbance at 420 nm
1	1	1 x 0.0833 / 100 = 0.000833	0.75
2	2	2 x 0.0833 / 100 = 0.001666	0.77
3	3	3 x 0.0833 / 100 = 0.002499	0.79
4	4	4 x 0.0833 / 100 = 0.003332	0.81
5	5	5 x 0.0833 / 100 = 0.004165	0.84
6	6	6 x 0.0833 / 100 = 0.004998	0.86


Calibration Plot
Absorbance
0.88
0.86
0.84
0.82
0.8
0.78
0.76
0.74
0.72
0
0.001
0.002
0.003
0.004
0.005
0.006
Concentration of Giloy, g


Calibration Plot
Absorbance
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
0.005
0.01
0.015
0.02
0.025
Concentration of Giloy, g

Syste m No	Absorb ance at 420 nm	Concentration of Giloy from graph, g	Volume of Giloy leaf solution taken, ml	Concentration of Giloy per100 ml, g	Average concentration of Giloy per 100 ml, g
7	0.68	-	1	-	0.3435
8	0.88	0.0056	2	100 x 0.0056 / 2 = 0.28	
9	1.04	0.0114	3	100 x 0.0114 / 3 = 0.38	
10	1.13	0.0145	4	100 x 0.0145 / 4 = 0.3625	
11	1.24	0.0185	5	100 x 0.0185 / 5 = 0.37	
12	1.27	0.0195	6	100 x 0.0195 / 6 = 0.325	

Hence 100 ml Giloy leaf solution contains 0.3435 g Giloy. Hence 2 Giloy leaf contains 0.3435 g Giloy. Hence 1 Giloy leaf will contain 0.3435 / 2 = 0.1718 g Giloy i.e., diverse phytochemicals, including alkaloids, phytosterols, glycosides, tinosporide, and other mixed chemical compounds.

2. FTIR study of Giloy Ghanvati medicinal sample

Spectral region wave number cm^{-1}	**Pattern and intensity of Band**	**Bond causing Absorption**	**Compound Class**
3940.57	Broad and low intensity	-	-
3900.07	Broad and low intensity	-	-
3857.63	Broad and low intensity	-	-
3836.42	Broad and low intensity	-	-
3741.90	Broad and low intensity	-	-
3369.64	Broad and strong intensity	O-H stretching	Alcohol
2926.01	Broad and strong intensity	O-H stretching N-H stretching	Carboxylic acid Amine salt
2360.87	Sharp and moderate intensity	-	-
2266.36	-	-	-
2140.99	Broad and low intensity	-	-
1950.03	-	-	-
1915.31	-	-	-
1703.14	Broad and strong intensity	C=O stretching	Conjugated acid
1612.49	Broad and strong intensity	C=C stretching	α, β- unsaturated ketone

1512.19	Broad and low intensity	-	-
1419.61	Broad and moderate intensity	O-H bending	alcohol
1367.53	Broad and moderate intensity	-	-
1203.58	-	-	-
1145.72	Broad and moderate intensity	-	-
1074.35	Broad and moderate intensity	-	-
1033.85	Broad and moderate intensity	-	-
929.69	Broad and low intensity	-	-
856.39	Broad and low intensity	-	-
763.81	Broad and low intensity	-	-
663.51	Broad and low intensity	-	-
569.00	Broad and low intensity	-	-
526.57	Broad and low intensity	-	-
460.99	Broad and low intensity	-	-
435.91	Broad and low intensity	-	-

CONCLUSION

1. Colorimetric phytochemical analysis of Tinospora Cordifolia (Giloy)

1 Giloy leaf contains 0.1718 g Giloy i.e., diverse phytochemicals, including alkaloids, phytosterols, glycosides, tinosporide, and other mixed chemical compounds.

2. FTIR study of Giloy Ghanvati medicinal sample

Interpretation of FTIR Spectra of Giloy Ghanvati medicinal sample shows presence of various functional groups such as O-H stretching - Alcohol, Carboxylic acid, O-H bending - Alcohol, N-H stretching - Amine salt, C=C stretching - α, β- unsaturated ketone and C=O stretching - Conjugated acid.

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61

Determination of Hydochloric Acid Neutralizing Capacity of Different Antacid Tablet by Back Titration Method and Its FTIR Analysis

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ABSTRACT

An antacid is a substance which neutralizes stomach acidity and is used to relieve heartburn, indigestion or an upset stomach. Several liquid antacid preparations are marketed. Common liquid preparations include milk of magnesia and magnesium/aluminum combinations. A potential advantage of using a liquid preparation over a tablet is that liquids may provide quicker relief, however this may coincide with a shorter duration of action. Chewable tablets are one of the most common forms of antacids, and are readily available over the counter. Upon reaching the stomach, the tablet powder will dissolve in the stomach acid, allowing the cations to be released and neutralize excess stomach acid. Common salts available in tablet form include those of calcium, magnesium, aluminum, and sodium. Effervescent tablets are tablets which are designed to dissolve in water, and then release carbon dioxide. Common ingredients include citric acid and sodium bicarbonate, which react when in contact with water to produce carbon dioxide. Effervescent antacids may also contain aspirin, sodium carbonate, or tartaric acid. Those containing aspirin may cause further gastric irritation and ulceration due to aspirin's effects on the mucous membrane of the stomach.

Present study deals with determination of Hydrochloric acid neutralizing capacity of an antacid tablets such as ACILOC 150, Athzol-DSR, Gelusil, NEXPRO-40, Omee-D, PAN-L, Pantafol-DSR, Rabesec-20, Rabifeel – LS and Rantac 150 using back titration method and FTIR study of Pantafol-DSR.

Antacid tablets contain bases like calcium carbonate, magnesium carbonate, magnesium hydroxide, sodium bicarbonate etc. The tablet can neutralize the HCl present in stomach and can decreases the acidity. The HCl neutralizing capacity of an antacid tablet can be determined by adding tablet to a known quantity of excess HCl then back titrating the unneutralized acid with standard alkali solution using phenolphthalein indicator. The higher the amount of Hydrocloric acid neutralized by Antacids, the better is the acid neutralizing capacity. The result shows that the tablet Rantac 150 has highest acid neutralizing capacity and PAN_L lowest acid neutralizing capacity. Rantac 150 >Rabifeel – LS > Omee-D > Pantafol-DSR > Rabesec-20 > NEXPRO-40 > Athzol-DSR > ACILOC 150 > Gelusil > PAN-L. The back titration method used in this study is simple, inexpensive and can be used in routine monitoring of the quality of Antacid tablets.

FTIR spectra of Pantafol-DSR is obtained at room temperature by using an FTIR Spectrophotometer – Perkin Elmer – Spectrum RX-IFTIR. The spectra is collected in a range from 400 to 4000 cm^{-1}. Interpretation of FTIR Spectra of Pantafol-DSR shows Presence of various functional groups such as C-H bending - Aromatic compound; O-H stretching – Alcohol, Carboxylic acid, C=O stretching - Conjugated acid, Conjugated aldehyde, C≡C stretching – Alkyne.

Keywords: Hydochloric Acid Neutralizing Capacity, Antacid Tablet, Back Titration Method, FTIR Analysis

INTRODUCTION

Antacid

An antacid is a substance which neutralizes stomach acidity and is used to relieve heartburn, indigestion or an upset stomach.[1] Some antacids have been used in the treatment of constipation and diarrhea.[2] Marketed antacids contain salts of aluminium, calcium, magnesium, or sodium.[2] Some preparations contain a combination of two salts, such as magnesium carbonate and aluminium hydroxide (e. g. hydrotalcite).[3] Antacids are available over the counter and are taken by mouth to quickly relieve occasional heartburn, the major symptom of gastroesophageal reflux disease and indigestion. Treatment with antacids alone is symptomatic and only justified for minor symptoms.[4] Alternative uses for antacids include constipation, diarrhea, hyperphosphatemia, and urinary alkalization.[5] Some antacids are also used as an adjunct to pancreatic enzyme replacement therapy in the treatment of pancreatic insufficiency.[6] Non-particulate antacids (sodium citrate) increase gastric pH with little or no effect on gastric volume, and therefore may see some limited use in pre-operative procedures. Sodium citrate should be given within 1 hour of surgery to be the most effective.[7] Conventional effervescent tablets contain a significant amount of sodium and are associated with increased odds of adverse cardiovascular events according to a 2013 study.[8] Alternative sodium-free formulations containing magnesium salts may cause diarrhea, whereas those containing calcium or aluminum may cause constipation. Rarely, long-term use of calcium carbonate may cause kidney stones. Long-term use of antacids containing aluminum may increase the risk of developing osteoporosis.[9] In vitro studies have found a potential for acid rebound to occur due to antacid overuse, however the significance of this finding has been called into question.[10][11] When an excess amount of acid is produced in the stomach, the natural mucous barrier that protects the lining of the stomach can degrade, leading to pain and irritation. There is also potential for the development of acid reflux, which can cause pain and damage to the esophagus. Antacids contain alkaline ions that chemically neutralize stomach gastric acid, reducing damage to the stomach lining and esophagus, and relieving pain.[1] Some antacids also inhibit pepsin, an enzyme that can damage the esophagus in acid reflux.[5][12] Antacids do not directly inhibit acid secretion, and thus are distinct from acid-reducing drugs like H2-receptor antagonists or proton pump inhibitors. Antacids do not kill the bacteria Helicobacter pylori, which causes most ulcers.[4] Antacids are known to interact with several oral medications, including fluoroquinolone and tetracycline antibiotics, iron, itraconazole, and prednisone.[13] Metal chelation is responsible for some of these interactions (e.g.fluoroquinolones, tetracyclines), leading to decreased absorption of the chelated drug. Some interactions may be due to the pH increase observed in the stomach following antacid ingestion, leading to increased absorption of weak acids, and decreased absorption of weak bases. Antacids also cause an increase in pH of the urine (alkalization), which may cause increased blood concentrations of weak bases, and increased excretion of weak acids.[14] A proposed method to mitigate the effects of stomach acidity and chelation on drug absorption is to space out the administration of antacids with interacting medications, however this method has not been well studied for drugs affected by urine alkalization.[13] There are concerns regarding interactions between delayed-release tablets and antacids, as antacids may increase the stomach pH to a point at which the coating of the delayed-release tablet will dissolve, leading to degradation of the drug if it is pH sensitive.[14] Antacids may be formulated with other active ingredients such as simethicone to control gas, or alginic acid to act as a physical barrier to acid.[15]

Several liquid antacid preparations are marketed. Common liquid preparations include milk of magnesia and magnesium/aluminum combinations. A potential advantage of using a liquid preparation over a tablet is that liquids may provide quicker relief, however this may coincide

with a shorter duration of action.[16] Chewable tablets are one of the most common forms of antacids, and are readily available over the counter. Upon reaching the stomach, the tablet powder will dissolve in the stomach acid, allowing the cations to be released and neutralize excess stomach acid. Common salts available in tablet form include those of calcium, magnesium, aluminum, and sodium.[13] Some common brand are Tums, Gaviscon chewable tablets, and Maalox chewable tablets.[17] Effervescent tablets are tablets which are designed to dissolve in water, and then release carbon dioxide.[18][19][20] Common ingredients include citric acid and sodium bicarbonate, which react when in contact with water to produce carbon dioxide. Effervescent antacids may also contain aspirin,[21] sodium carbonate, or tartaric acid.[22] Those containing aspirin may cause further gastric irritation and ulceration due to aspirin's effects on the mucous membrane of the stomach.[23] Common brands include Alka-Seltzer, Gaviscon, and Eno.

Study based on the evaluation of acid neutralizing capacity of five different commercial brands of antacid tablets was done. [24] Antacids are commonly used as over - the - counter (OTC) drugs or prescribed medications. Some antacid products may neutralize more acid in the stomach than others. The ability of an antacid to neutralize acid is expressed as its Acid Neutralizing Capacity (ANC). Study was undertaken with the objective of assessing the quality of different brands of antacid tablets. The assessment parameters included the evaluation of uniformity of weight, uniformity of thickness, crushing strength, friability, as well as the ANC (using pH and titrimetric method), which is easy to use, accurate, reproducible, simple, and inexpensive. [25] Study has been evaluated the acid neutralizing and buffering capacities (BC) of nine selected antacid brands ("L1-L9") in Ghana. [26] Gastric acidity is highly prevalent in the Indian Population. People usually take commercially available antacids to alleviate the symptoms. Unfortunately, the use of these over the counter drugs has been so common that they are vastly overused and are taken even for mild heartburn or indigestion, which makes the underlying problem worse. The study aimed at identifying common traditional remedies used in India to treat acidity and to evaluate their acid neutralizing capacity; and compare it with their commercially available counterparts. The acid neutralizing capacities of the traditional remedies were analyzed by Back titration method. [27] The study was aimed to evaluate the acid-neutralizing capacity (ANC) and other properties of antacid drugs marketed in Morocco. Other properties such as price and sodium content were also studied. [28]

Present study deals with determination of Hydrochloric acid neutralizing capacity of an antacid tablets such as ACILOC 150, Athzol-DSR, Gelusil, NEXPRO-40, Omee-D, PAN-L, Pantafol-DSR, Rabesec-20, Rabifeel – LS and Rantac 150 using back titration method and FTIR study of Pantafol-DSR. Antacid tablets contain bases like calcium carbonate, magnesium carbonate, magnesium hydroxide, sodium bicarbonate etc. The tablet can neutralize the HCl present in stomach and can decreases the acidity. The HCl neutralizing capacity of an antacid tablet can be determined by adding tablet to a known quantity of excess HCl then back titrating the unneutralized acid with standard alkali solution using phenolphthalein indicator. The higher the amount of Hydrocloric acid neutralized by Antacids, the better is the acid neutralizing capacity. The result shows that the tablet Rantac 150 has highest acid neutralizing capacity and PAN_L lowest acid neutralizing capacity value. Rantac 150 >Rabifeel – LS > Omee-D > Pantafol-DSR > Rabesec-20 > NEXPRO-40 > Athzol-DSR > ACILOC 150 > Gelusil > PAN-L. The back titration method used in this study is simple, inexpensive and can be used in routine monitoring of the quality of Antacid tablets. FTIR spectra of Pantafol-DSR is obtained at room temperature by using an FTIR Spectrophotometer – Perkin Elmer – Spectrum RX-IFTIR. The spectra is collected in a range from 400 to 4000 cm^{-1}. Interpretation of FTIR Spectra of Pantafol-DSR shows Presence of various functional groups such as C-H bending - Aromatic

compound; O-H stretching – Alcohol, Carboxylic acid, C=O stretching - Conjugated acid, Conjugated aldehyde, C≡C stretching – Alkyne.

METHODOLOGY

1. Determination of Hydrochloric acid neutralizing capacity of an antacid tablet

Antacid tablets contain bases like calcium carbonate, magnesium carbonate, magnesium hydroxide, sodium bicarbonate etc. The tablet can neutralize the HCl present in stomach and can decreases the acidity. The HCl neutralizing capacity of an antacid tablet can be determined by adding tablet to a known quantity of excess HCl then back titrating the unneutralized acid with standard alkali solution using phenolphthalein indicator.

$$CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2O + CO_2(g)$$
$$MgCO_3 + 2HCl \rightarrow MgCl_2 + H_2O + CO_2$$
$$Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$$
$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$$

The above reactions are common reactions between an antacid in which main ingredients are $CaCO_3$, $MgCO_3$, $Mg(OH)_2$, $NaHCO_3$ and stomach HCl

$$\text{Excess HCl} + NaOH \rightarrow NaCl + H_2O$$

Preparation of 0.1 M Oxalic acid solution: 0.1 M Oxalic acid solution was prepared by dissolving 0.63 g oxalic acid with distilled water in 100 ml volumetric flask and volume was made upto 100 ml mark with distilled water.

Preparation of 0.1 M Sodium hydroxide solution: 0.1 M Sodium hydroxide solution was prepared by dissolving 4 g sodium hydroxide with distilled water in 1 litre volumetric flask and volume was made upto 1litre mark with distilled water.

Preparation of 0.1 M Hydrochloric acid solution: 0.1 M Hydrochloric acid solution was prepared by diluting 8.3 ml of 12 M Hydrochloric acid with distilled water in 1 litre volumetric flask and volume was made upto 1litre mark with distilled water.

Standardization of Sodium hydroxide solution: 10 ml of 0.1 M Oxalic acid solution was taken in 100 ml conical flask to it 3 drops of phenolphthalein indicator was added and solution was titrated with Sodium hydroxide solution until it turns pink which persisted for at least 30 seconds. The volume of Sodium hydroxide solution was recorded. The titration procedure was repeated 2 more times and the constant titre value was recorded.

Standardization of Hydrochloric acid solution: 10 ml of Hydrochloric acid solution was taken in 100 ml conical flask to it 3 drops of phenolphthalein indicator was added and solution was titrated with Sodium hydroxide solution until it turns pink which persisted for at least 30 seconds. The volume of Sodium hydroxide solution was recorded. The titration procedure was repeated 2 more times and the constant titre value was recorded.

Determination of Hydrochloric acid neutralizing capacity of an antacid tablet: One Antacid tablet of Pantafol-DSR, Omee-D, Rabifeel – LS, Rantac 150, Gelusil, Athzol-DSR, PAN-L, Rabesec-20, ACILOC 150 and NEXPRO-40 were crushed in mortal and pestle. 0.5 g crushed tablet was transferred into 250 ml conical flask. To it 75 ml 0.1 N HCl was added and

solution was heated to boil and dissolve the crushed tablet for 5 minutes then cooled and to it 3 drops of phenolphthalein indicator was added and solution was titrated with Sodium hydroxide solution until it turns pink which persisted for at least 30 seconds. The volume of Sodium hydroxide solution was recorded. The titration procedure was repeated 2 more times and the average titre value was recorded. Molarity of HCl in reaction mixture after neutralization with Antacid tablet was calculated. From which difference in Molarity of HCl, weight of HCl neutralized by Antacid Tablet per litre, weight of HCl neutralized by Antacid Tablet per 75 ml and weight of HCl neutralized by 1 g Antacid tablet was calculated.

2. FTIR study of Pantafol-DSR

FTIR can be routinely used to identify the functional groups and identification/quality control of raw material/finished products. Spectrum RX-I offers fast throughput and rapid access to reliable and dependable IR results. High signal to noise ratio makes FTIR more useful for difficult samples. It has resolution of 1 cm1 and scan range of 4000 cm-1 to 250 cm-1. In the normal mode around 10 mg sample is required in the form of fine powder. The sample can be analyzed in the form of liquid, solid and thin films also.

FTIR spectra of Pantafol-DSR is obtained at room temperature by using an FTIR Spectrophotometer – Perkin Elmer – Spectrum RX-IFTIR. The spectra is collected in a range from 400 to 4000 cm^{-1}.

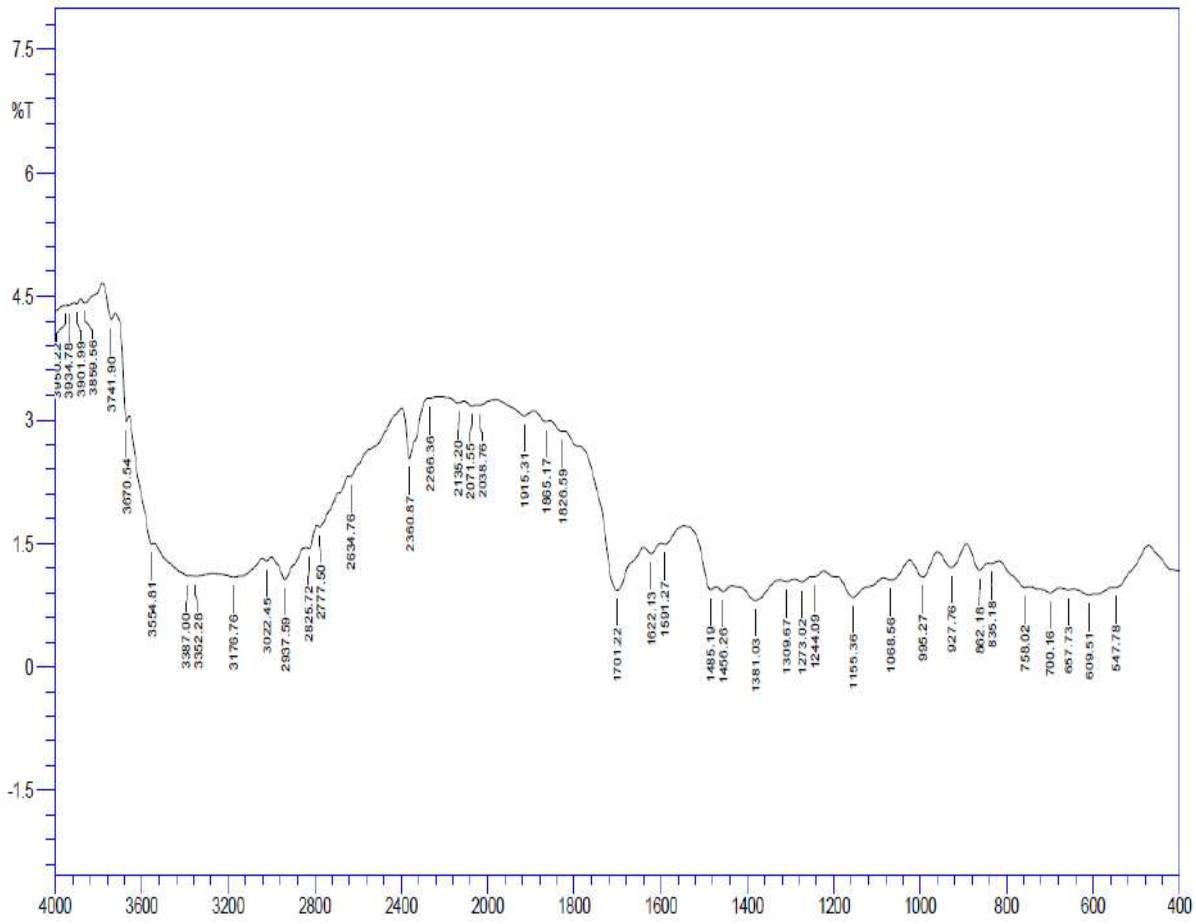


Figure 1. FTIR spectra of Pantafol-DSR

RESULTS AND DISCUSSION

1. Determination of Hydrochloric acid neutralizing capacity of an antacid tablet

Standardization of Sodium hydroxide solution:

Volume of 0.1 M Oxalic acid solution taken, ml	Volume of Sodium hydroxide solution required, ml	Constant titre value
10	10.0	10.1
10	10.1	
10	10.1	

Standardization of Hydrochloric acid solution:

Volume of Hydrochloric acid solution taken, ml	Volume of Sodium hydroxide solution required, ml	Constant titre value
10	10.0	9.9
10	9.9	
10	9.9	

Determination of Hydrochloric acid neutralizing capacity of an antacid tablet:

Molarity of Oxalic acid = 0.63 x 10 / 63 = 0.1

Molarity of Sodium hydroxide solution = 0.1 x 10 / 10.1 = 0.099

Molarity of Hydrochloric acid solution = 0.099 x 9.9 / 10 = 0.098

Table 1. Determination of Hydrochloric acid neutralizing capacity of an antacid tablet

Name of Antacid Tablet	Constant titre value, ml	Molarity of HCl in reaction mixture after neutralization with Antacid tablet	Difference in Molarity of HCl	Weight of HCl neutralized by Antacid Tablet perliter, g	Weight of HCl neutralized by Antacid Tablet per 75 ml, g	Weight of HCl neutralized by 1 g Antacid tablet, g
ACILOC 150	12	0.099 x 12 / 75 = 0.0158	0.098 – 0.0158 = 0.0822	0.0822 x 36.5 = 3.0003	3.0003 x75 / 1000 = 0.2250	0.2250 x 1 / 0.5 = 0.45
Athzol-DSR	10.5	0.099 x 10.5 / 75 = 0.0139	0.098 – 0.0139 = 0.0841	0.0841 x 36.5 = 3.0697	3.0697 x75 / 1000 = 0.2302	0.2302 x 1 / 0.5 = 0.4604
Gelusil	14.5	0.099 x 14.5 / 75 = 0.0191	0.098 – 0.0191 = 0.0789	0.0789 x 36.5 = 2.8799	2.8799 x75 / 1000 = 0.2160	0.2160 x 1 / 0.5 = 0.432
NEXPRO-40	8.6	0.099 x 8.6 / 75 = 0.0114	0.098 – 0.0114 = 0.0866	0.0866 x 36.5 = 3.1609	3.1609 x75 / 1000 = 0.2371	0.2371 x 1 / 0.5 = 0.4742
Omee-D	2.1	0.099 x 2.1 / 75 = 0.0028	0.098 – 0.0028 = 0.0952	0.0952 x 36.5 = 3.4748	3.4748 x75 / 1000 = 0.2606	0.2606 x 1 / 0.5 = 0.5212
PAN-L	16	0.099 x 16 / 75 = 0.0211	0.098 – 0.0211 = 0.0769	0.0769 x 36.5 = 2.8069	2.8069 x75 / 1000 = 0.2105	0.2105 x 1 / 0.5 = 0.421
Pantafol-DSR	4.8	0.099 x 4.8 / 75 = 0.0063	0.098 – 0.0063 = 0.0917	0.0917 x 36.5 = 3.3471	3.3471 x75 / 1000 = 0.2510	0.2510 x 1 / 0.5 = 0.502

Rabesec-20	6.5	0.099 x 6.5 / 75 = 0.0086	0.098 – 0.0086 = 0.0894	0.0894 x 36.5 = 3.2631	3.2631 x75 / 1000 = 0.2447	0.2447 x 1 / 0.5 = 0.4894
Rabifeel - LS	1	0.099 x 1 / 75 = 0.0013	0.098 – 0.0013 = 0.0967	0.0967 x 36.5 = 3.5296	3.5296 x75 / 1000 = 0.2647	0.2647 x 1 / 0.5 = 0.5294
Rantac 150	0.5	0.099 x 0.5 / 75 = 0.0007	0.098 – 0.0007 = 0.0973	0.0973 x 36.5 = 3.5515	3.5515 x75 / 1000 = 0.2664	0.2664 x 1 / 0.5 = 0.5328

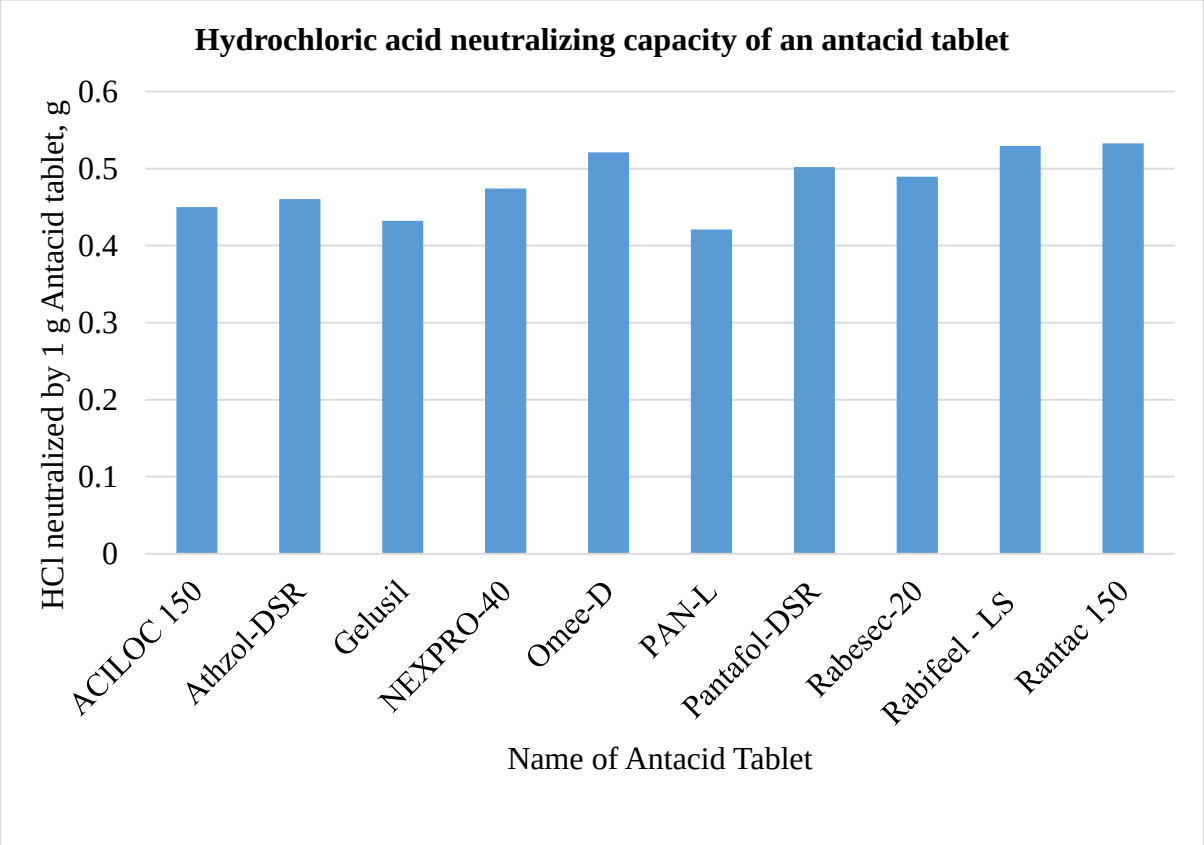


Figure 2 Hydrochloric acid neutralizing capacity of an antacid tablet

Hydrochloric acid neutralizing capacity of commercial antacid tablets are summerized in Table 1 and graphically depicted in Figure 2.

2. FTIR study of Pantafol-DSR

Interpretation of FTIR Spectra of Pantafol-DSR can be done as follows:

Spectral region wave number cm^{-1}	Pattern and intensity of Band	Bond causing Absorption	Compound Class
3950.22	Broad and low intensity	-	-
3934.78	Broad and low intensity	-	-
3901.99	Broad and low intensity	-	-

3859.56	Broad and low intensity	-	-
3741.90	Broad and low intensity	-	-
3670.54	Sharp and moderate intensity	O-H stretching	Alcohol
3554.81	Broad and strong intensity	O-H stretching	Alcohol
3387.00	Broad and strong intensity	O-H stretching	Alcohol
3352.28	Broad and strong intensity	O-H stretching	Alcohol
3176.76	Broad and strong intensity	O-H stretching	Carboxylic acid
3022.45	Broad and strong intensity	O-H stretching	Carboxylic acid
2937.59	Broad and strong intensity	O-H stretching	Carboxylic acid
2825.72	Broad and strong intensity	O-H stretching	Carboxylic acid
2777.50	Broad and strong intensity	O-H stretching	Carboxylic acid
2634.76	Broad and strong intensity	O-H stretching	Carboxylic acid
2360.87	Sharp and moderate intensity	-	-
2266.36	Broad and low intensity	-	-
2135.20	Broad and low intensity	C≡C stretching	Alkyne
2071.55	Broad and low intensity	-	-
2038.76	Broad and low intensity	-	-
1915.31	Broad and low intensity	C-H bending	Aromatic compound
1865.17	Broad and low intensity	C-H bending	Aromatic compound
1826.59	Broad and low intensity	C-H bending	Aromatic compound
1701.22	Broad and strong intensity	C=O stretching C=O stretching	Conjugated acid Conjugated aldehyde
1622.13	Broad and low intensity	-	-
1591.27	Broad and low intensity	-	-
1485.19	Broad and moderate intensity	-	-
1456.26	Broad and moderate intensity	-	-
1381.03	Broad and low intensity	-	-
1309.67	Broad and low intensity	-	-
1273.02	Broad and low intensity	-	-

1244.09	Broad and low intensity	-	-
1155.36	Broad and low intensity	-	-
1068.56	Broad and low intensity	-	-
995.27	Broad and low intensity	-	-
927.76	Broad and low intensity	-	-
862.18	Broad and low intensity	-	-
835.18	Broad and low intensity	-	-
758.02	Broad and low intensity	-	-
700.16	Broad and low intensity	-	-
657.73	Broad and low intensity	-	-
609.51	Broad and low intensity	-	-
547.78	Broad and low intensity	-	-

CONCLUSION

1. Determination of Hydrochloric acid neutralizing capacity of an antacid tablet

The higher the amount of Hydrocloric acid neutralized by Antacids, the better is the acid neutralizing capacity. The result shows that the tablet Rantac 150 has highest acid neutralizing capacity and PAN_L lowest acid neutralizing capacity value. Rantac 150 >Rabifeel – LS > Omee-D > Pantafol-DSR > Rabesec-20 > NEXPRO-40 > Athzol-DSR > ACILOC 150 > Gelusil > PAN-L. The back titration method used in this study is simple, inexpensive and can be used in routine monitoring of the quality of Antacid tablets.

2. FTIR study of Pantafol-DSR

Interpretation of FTIR Spectra of Pantafol-DSR shows Presence of various functional groups such as C-H bending - Aromatic compound; O-H stretching – Alcohol, Carboxylic acid, C=O stretching - Conjugated acid, Conjugated aldehyde, C≡C stretching – Alkyne.

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62

Investigation of Physico-chemical parameters of groundwater from Barshitakli tehsil region, Akola district, Maharashtra, India

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ABSTRACT

This investigation determines the ground water quality of regions in Barshitakli tehsil, Akola district in Maharashtra. Samples collected from various bore wells that were used for drinking purposes. The physico-chemical parameters such as Electrical conductivity, pH, Total hardness, Mg hardness, Ca hardness, Mg++ ions, Ca++ ions and Chloride ion were investigated to determine the present condition of the groundwater quality during the periods from December 2020 to December 2021 (consecutive post monsoon and pre monsoon). Overall ground water quality of Barshitakli tehsil region is unsafe for human being. The groundwater samples of bore well from Alanda and Januna village has the Turbidity beyond prescribed limits of drinking water (IS:10500). The post monsoon sample shows increase in the values of physio-chemical parameters of these two villages were due to higher erosion of soil. The advanced farming and excessive use of chemical fertilizer and pesticides might has resulted in the contamination of ground water.

Keywords: Physico-chemical, groundwater, Electrical conductivity, Turbidity, contamination.

INTRODUCTION

Potable water is also called as life and it has less abundance on the earth. Almost all life processes on earth require water. The 71% of area on the earth's crust is occupied by water but earth's 97% of water is present in the oceans which is too salty for drinking, growing crops and for industrial purposes. The water to be describe as potable, the certain physical, chemical and microbiological standards should be designed so as to ensure the water is potable and safe for drinking (Tebutt, 1993 and Oladipo and Adeboye, 2015). Most of the industries discharge their effluent without proper treatment into nearby open pits or pass them through unlined channels, resulting in the contamination of ground water (Rao and Mamatha, 2004, Mahanta et. al., 2015, Pande et. al., 2010). Potable water should be free from disease causing chemical substances and micro-organisms to health (Ihekoronye and Ngoddy, 1985). The majority of fresh water is existing in the ground in the form of soil moisture and beneath the ground in aquifers.

The aim of present investigation is to study the groundwater samples collected from bore well so as to understand the physico-chemical parameters of water in the Barshitakli tehsil region, Akola district, Maharashtra.

STUDY AREA

Barshitakli is a taluka located in Akola district of Maharashtra. It is one of 7 Talukas of Akola district. There are 159 villages in Barshitakli Taluka. The total area of Barshitakli is 812.97 sq.km with population density of 184 per sq.km.

MATERIAL AND METHODS

The water samples from Barshitakli tehsil were collected from bore wells of ten different villages. Water sample were collected in poly bottle during each consecutive month. Physico- chemical parameters like water temperature, pH and transparency were recorded immediately at the time of sample collection by using thermometer, portable digital pH meter and transparency was measured with the help of Secchi disc respectively. The samples were then transferred to laboratory for further analysis. The Parameters Such as TDS, Hardness and chlorides were estimated in the Laboratory by using standard Methods as prescribed by APHA.

SAMPLE COLLECTION

Ground water samples were collected from ten (10) bore wells at various locations within study area during pre and post monsoon season. Details of sampling locations are along with their co-ordinates illustrated in Table1.

PHYSICO-CHEMICAL ANALYSIS OF GROUND WATER

The collected samples were analyzed for different physico-chemical parameters such as pH, Electrical conductivity, Turbidity, TDS, Total hardness, Ca hardness, Mg hardness, Ca ion, Mg ion, Chloride, and Temperature as per the standard methods (APHA, 1998) and the results were compared with the Indian Standards (IS: 10500) for potable water.

RESULTS AND DISCUSSION

The water quality analysis of different ground water samples has been carried out for pH, Electrical conductivity, TDS, Total hardness, Ca hardness, Mg hardness, Ca ion, Mg ion, Chloride, and Temperature. The status of water quality of these ground water sources is given in table 2.

Table 1: Sampling location and their coordinates

Sampling Location Area Code	Location	Co-ordinates
GW1	Alanda	20.712456, 77.333320
GW2	Barshitakli	20.685510, 77.284157
GW3	Bhendi Mahal	20.666653, 77.268490
GW4	Chincholi Rudrayani	20.832091, 77.544832
GW5	Dagadparwa	20.730045, 77.404649
GW6	Dhaba	20.661896, 77.355489
GW7	Donad BK.	20.654725, 77.302891
GW8	Januna	20.694452, 77.254599
GW9	Kanheri	20.709671, 77.234655
GW10	Mahan	20.700926, 77.321669

Table 2: Showing status of water quality of these ground water sources

Area code	pH		Turbidity (cm)		Conductance (µmhos/cm)		Total Hardness (mg/l)		TDS (mg/l)		Ca I on (mg/l)		Mg Ion (mg/l)		Chloride (mg/l)		Temp °C	
	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po
GW1	7.3	8.0	11.2	16.5	120	180	170	210	468	450	80	180	72	54	120	140	26	22
GW2	6.7	7.2	5.6	6.5	170	210	180	215	450	509	72	250	74	62	160	164	27	24
GW3	6.9	7.1	3.2	5.2	160	230	210	284	480	450	78	260	68	81	142	155	24	27
GW4	7.3	6.8	4.1	5.6	133	270	210	246	502	457	97	240	87	46	155	190	25	21
GW5	7.2	7.2	2.8	4.3	125	166	240	246	350	605	68	210	72	72	86	120	28	23
GW6	6.3	7.4	3.5	7.1	125	188	250	290	498	544	65	150	64	64	182	20	29	24
GW7	7.2	6.9	3.5	4.7	142	200	270	285	609	807	54	168	68	52	163	190	25	24
GW8	7.1	7.8	8.2	13.2	126	198	286	290	568	402	80	125	64	45	54	144	24	26
GW9	7.5	7.6	4.9	6.1	146	210	244	302	390	512	61	230	81	65	144	203	26	24
GW10	7.4	7.6	7.9	9.5	180	234	246	325	480	562	60	200	54	45	200	256	24	22
Mean	7.225		6.68		175.65		269.3		267.05		136.4		64.5		149.4		23.5	
IS: 10500	**6.5- 8.5**		**5.0-10***		----------		**300-600**		**500-2000***		**75-200***		**30-100***		**250-1000***		--	
Pr- Pre-Monsoon, Po-Post Monsoon																		

Finding of the present investigation is as follows-

1. The pH value found permissible limit as per IS: 10500 of all samples.
2. Turbidity of samples from Alanda (GW1) and Januna (GW8) found 16.5 and 13.6 respectively which is the not in permissible limits as per IS: 10500.
3. Electrical conductivity varied between 120 to 180 µmhos/cm to 180 to 270 µmhos/cm in pre and post monsoon season.
4. The same trend was observed in the case of total hardness of various ground water sources. It varied from 170 to280 mg/l and 210 to 325 mg/l in pre and post monsoon respectively.
5. TDS in all the samples were found to be within standard limits (IS:10500). In few samples the ions of calcium have crossed the standard limit (IS: 10500) during post monsoon season.
6. Chloride content of the ground water samples of hand pump were found to be within limit during in the range pre and post monsoon season respectively.
7. Temperature of the various ground water samples were noted to be from 24-29 ^{o}C and 21-26 ^{o}C during pre and post monsoon season respectively.

CONCLUSION

Overall ground water quality of Barshitakli tehsil region is unsafe for human being. The groundwater samples of bore well from Alanda and Januna village has the Turbidity beyond prescribed limits of drinking water (IS:10500). The post monsoon sample shows increase in the values of physio-chemical parameters of these two villages were due to higher erosion of soil. The advanced farming and excessive use of chemical fertilizer and pesticides might has resulted in the contamination of ground water.

Conflicts of interest: The authors stated that no conflicts of interest.

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63

Identification of confluence of multiple scaffolds required for Aurora Kinase A inhibition

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Abstract:
A vital signaling kinase with a significant function in cell division is Aurora Kinase A (AKA). Therefore, inhibiting AKA is a desirable strategy to reduce cancer. Herein, we report a QSAR (Quantitative Structure-Activity Relationships) analysis based on a set of 892 structurally different AKA inhibitors to explore the features governing AKA inhibition. A QSAR model with high statistical performance was created as per OECD (Organisation for Economic Co-operation and Development) guidelines (R2tr = 0.794, Q2LOO = 0.787, R2ex = 0.778, CCCex = 0.880). Predictive QSAR (external predictive ability) and Mechanistic QSAR (mechanistic interpretations) are well-balanced in the recently developed QSAR model, which is based on a set of eight variables. The present QSAR analysis is successful in identifying not only obscure and obvious structural features, but also the reported and unpublished pharmacophoric characteristics. The present research suggests that non-ring nitrogen atoms in combination with planer nitrogen and non-ring oxygen must exist at a precise distance from one another. Furthermore, the limit for simultaneous existence of sp^2 oxygen with sp^3 carbon and ring oxygen is a new feature identified in the present work.

Introduction:
The mitotic machinery, also known as cell division mechanism, is profoundly regulated[1]. Any abnormality or defect in mitosis produces nondiploid DNA, which eventually leads to cancer. The development of cancer chemotherapy drugs that specifically target centrosome maturation and separation, mitotic spindle assembly, chromosomal segregation, and cytokinesis has therefore attracted the attention of researchers. These processes involve the crucial role of several signaling kinases, such as Aurora[2], Plk (Polo-like kinase), and Cdk (cyclin-dependent kinase), to name a few. The Aurora kinase family of serine/threonine kinases is essential for the reliable accomplishment of mitosis[3]. Therefore, these kinases have drawn a lot of attention since their discovery in 1995 and the early identification of their expression in human cancer tissue in 1998. The present involves QSAR analysis to identify important structural features.

Methodology:
The structures were downloaded from ChEMBL (https://www.ebi.ac.uk/chembl/) for further analysis. The next step involves conversion of SMILES notation to 3D-optimized structure using MMFF94 (Cut-off: 0.01). Then, the molecular descriptors were calculated using PyDescriptor[4] and PaDEL[5]. Before actual feature selection, descriptor pruning was accomplished. After getting the reduced pool of descriptor GA-MLR was used for model building. After that, the model was validated using different parameters.

Results and Discussion:
The eight parametric model along with its statistical validation is as following:

Model-A:

	Estimate	Std. Error	t value	Pr(>|t|)	Conf.Int.(+/-95%)
(Intercept)	7.521	0.0314	239.8884	0	0.0616
fringOH6B	0.334	0.0204	16.3689	0	0.0401
fnotringNplaN3B	1.1305	0.0453	24.9618	0	0.0889
fsp2Osp3C4B	0.4022	0.0338	11.8862	0	0.0664
fnotringOnotringN5B	0.4113	0.0546	7.527	0	0.1073
r_ringO_sp2O	-0.9131	0.0796	-11.4699	0	0.1563
r_sp3C_sp2O	-0.1813	0.0089	-20.431	0	0.0174
KRFPC992	-0.7937	0.0361	-21.9712	0	0.0709
KRFPC3612	-1.7261	0.0679	-25.4162	0	0.1333

Statistical parameters associated with Model-A:

S.N.	Parameter	Value	S.N.	Parameter	Value
1.	R2_tr	0.7941	20.	RMSE_ex	0.5129
2.	Adj-R2	0.7918	21.	PRESS_ex	47.0818
3.	F(8-704)	339.4136	22.	Q2F1	0.7674
4.	RSS_tr	154.2898	23.	Q2F2	0.7661
5.	MSE_tr	0.2164	24.	Q2F3	0.7497
6.	RMSE_tr	0.4652	25.	MAE_ex	0.4328
7.	MAE_tr	0.3911	26.	K	1.0069
8.	s	0.4681	27.	K_prime	0.9881
9.	AIC	952.0537	28.	R2ext	0.7782
10.	BIC	997.7485	29.	CCC_ex	0.8802
11.	CCC_tr	0.8852	30.	r2m_ExPy	0.6736
12.	Q2_cv	0.7872	31.	r2m_EyPx	0.701
13.	RMSE_cv	0.473	32.	R2o	0.7683
14.	MSE_cv	0.2237	33.	R2o_dash	0.7601
15.	PRESS_cv	159.498	34.	Clos_dash	0.0232
16.	MAE_cv	0.3969	35.	Clos	0.0126
17.	R2_Yscr	0.011	36.	r2m_avg	0.6873
18.	MSE_ex	0.263	37.	r2m_delta	0.0273
19.	Training Set Compounds	713	38.	Prediction Set Compounds	179

The details of descriptors are as following:

Descriptor	Details	Software used
fringOH6B	Frequency of occurrence of hydrogen exactly at six bonds from ring oxygen	PyDescriptor
fnotringNplaN3B	Frequency of occurrence of planer nitrogen exactly at three bonds from non-ring nitrogen	PyDescriptor
fsp2Osp3C4B	Frequency of occurrence of sp3-hybridized carbon exactly at four bonds from sp2-hybridized oxygen	PyDescriptor

fnotringOnotringN5B	Frequency of occurrence of non-ring nitrogen exactly at five bonds from non-ring oxygen	PyDescriptor
r_ringO_sp2O	Ratio of ring oxygen to sp2-hybridized oxygen	PyDescriptor
r_sp3C_sp2O	Ratio of sp3-carbon to sp2-hybridized oxygen	PyDescriptor
KRFPC992	[!#1][NH]c1[cH][cH][cH]c([!#1])[cH]1 Meta-substituted aniline ring	PaDEL
KRFPC3612	Cc1ccn[nH]1 3-substituted pyrazole moiety	PaDEL

Model-A contains eight molecular descriptors covering broad chemical space. Four of the eight descriptors, namely fringOH6B, fnotringNplaN3B, fsp2Osp3C4B, and fnotringOnotringN5B, have positive coefficients in model-A, suggesting that augmenting their value could result in a better inhibition of AKA. The opposite is true for the four remaining descriptors, r_ringO_sp2O, r_sp3C_sp2O, KRFPC992, and KRFPC3612. It is to be noted that every molecular descriptor is a mathematical (or numeric) representation of one or more pharmacophoric features that control the biological profile. Further, the final biological activity (say IC50, Ki, etc.) of a molecule varies with multiple pharmacophore features and not by a single feature. In other words, the biological activity is the result of a confluence of various structural characteristics and some unidentified elements. Some characteristics are in charge of enhancing the desired pharmacological action, while others are responsible for reversing it. It is thought that the biological activity is determined concurrently by two or more pharmacophoric groups (Pharmacophore synergism).

Conclusion:

The present research suggests that non-ring nitrogen atoms in combination with planer nitrogen and non-ring oxygen must exist at a precise distance from one another. Furthermore, the limit for simultaneous existence of sp2 oxygen with sp3 carbon and ring oxygen is a new feature identified in the present work. In conclusion, the AKA inhibitory activity is associated with a group of structural features.

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64

Synthesis, Characterization and Biological Evaluation of 4-(4-Bromo-1-Hydroxy Naphthalen-2-Yl)-6-(4-Hydroxy Phenyl)-5,6-Dihydropyrimidine-2(1h)-One

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ABSTRACT: -

1-(4-Bromo-1-hydroxynaphthalen-2-yl)-ethan-1-one was prepared by refluxing 4-bromonaphthalen-1-ol with glacial acetic acid in presence of fused $ZnCl_2$. By condensing 1-(4-bromo-1-hydroxynaphthalen-2-yl)-ethan-1-ones with 4-Hydroxy benzaldehyde, to prepared by 1-(4- bromo -1- hydroxynaphthalen-2-yl)-3-(4-Hydroxy phenyl)-prop-2-en-1-one were synthesized.1-(4- bromo -1-hydroxynaphthalen-2-yl)-3-(4-Hydroxy phenyl)-prop-2-en-1-one, urea and concentrated HCl in DMF were added and refluxed. Cool and pour in crushed ice. Treat it with cold NH4OH solution to obtain titled compounds. The compounds thus synthesized have been characterized by physical and spectral data. All of these titled synthesized compounds have been screened for antimicrobial study and are found to possess excellent antimicrobial activities.

KEYWORDS: - antimicrobial activities, cold NH_4OH solution, concentrated HCl in DMF.

INTRODUCTION: -

Dihydropyrimidin-2(1H)-one are classified as hetero-cyclic compound and containing pyrimidine ring which is containing two nitrogen atoms in the six-member ring. Dihydropyrimidine are the most important heterocyclic ring system which play an important role in the synthesis of DNA and RNA. They widely using multi-component reaction like Biginelli reaction. In the field of heterocyclic chemistry dihydropyrimidine-2(1H)-one was synthesized through the one -pot condensation of an aromatic aldehyde and urea in the presence of the basic [1-3]. Dihydropyrimidines are one of the important heterocyclic compounds, which are of interest due to its efficiency towards various pharmacological uses [4]. The synthesis of the dihydropyridine and their derivatives increasing tremendously significant because they generally show diverse medicinal properties [5]. Newly researcher goal dihydropyrimidine derivatives modulated heat shock responses and have neuroprotective responses such like that optimized for their ability to modulate cellular stress responses based on favorable toxicological data [6]. Many aryls substituted dihydropyrimidine-2-one are found to exhibited biological activities [7]. Many reports exploring in Vivo and in Vitro dihydropymidine-2-one derivatives show variety of pharmacological activities such as active and safe tumor anti-initiating and multi-potent blocking agent [8], anxiolytic [9], antihypertensive agents [10], anticonvulsant [11], anticancer [12], analgesic activities [13], anti-bacterial [14], channel blockers [15], anti-HIV [16].

Their efforts are quite significant in literature hence considering the scope of dihydropyrimidine derivatives we have synthesized novel4-(4-bromo-1-hydroxynaphthalen-2-yl)-6-(4-hydroxy phenyl)-5,6-dihydropyrimidine-2(1h)-one from 4- bromonaphthalen-1-ol and studied for their biological activities.

MATERIALS AND METHOD: -

Synthesis of 1-(4-Bromo-1-hydroxynaphthalen-2-yl)-ethan-1-one.

1-(4-Bromo-1-hydroxynaphthalen-2-yl) ethan-1-one was prepared by modified Nenchis method in which 4-bromo- naphthalen-1-ol was refluxed with glacial acidic acid in presence of fused $ZnCl_2$.

Synthesis of 1-(4-Bromo-1-hydroxynaphthalen-2-yl)-3-(4-Hydroxy phenyl)-prop-2-en-1-one.

1-(4-Bromo-1-hydroxynaphthalen-2-yl)-3-(4-Hydroxy phenyl)-prop-2-en-1-one were synthesized from 1-(4-Bromo-1-hydroxynaphthalen-2-yl) ethan-1-one by condensing it with 4-Hydroxy benzaldehyde were added in ethanol solvent and KOH mixture.

Synthesis of 4-(4-Bromo-1-hydroxy naphthalen-2-yl)-6-(4-Hydroxy phenyl)-5,6-dihydropyrimidine-2(1H)-one.

4-(4-Bromo-1-hydroxy naphthalen-2-yl)-6-(4-methoxy phenyl)-5,6-dihydropyrimidine-2(1H)-one were prepared from 1-(4-Bromo-1-hydroxynaphthalen-2-yl)-3-(4-Hydroxy phenyl)-prop-2-en-1-one was reflux with urea and concentrated HCl in DMF. It was then treated with cold NH_4OH.

In present work the compounds under investigation are: -

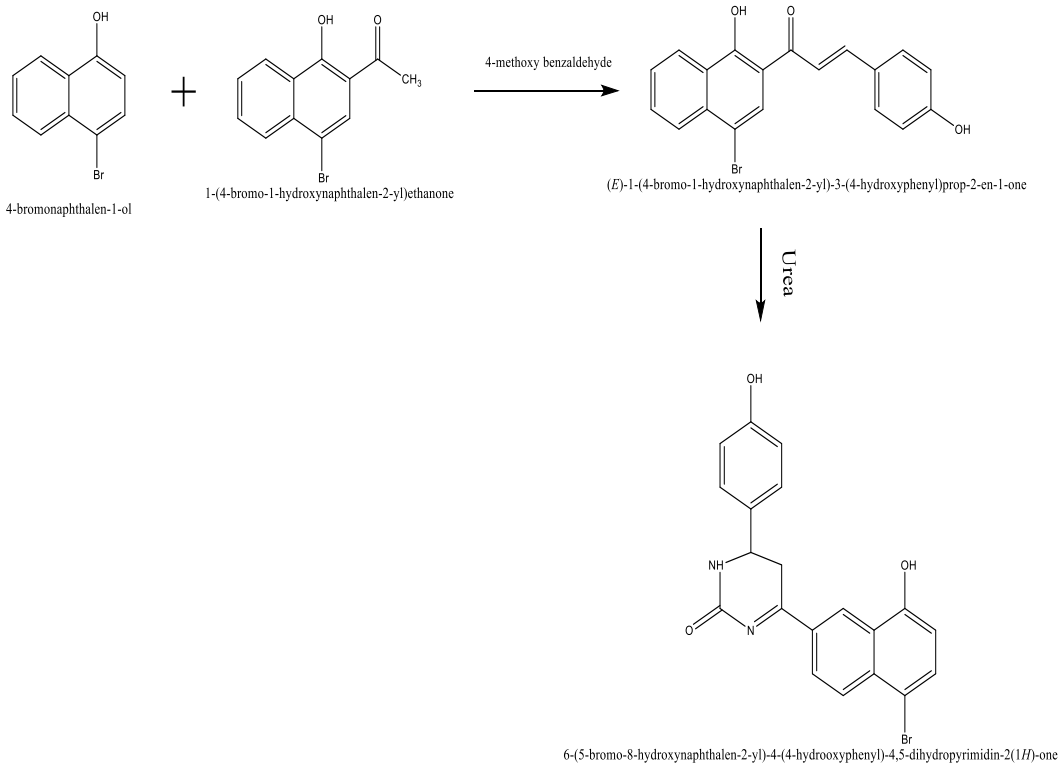
Compound 1: 4-(4-Bromo-1-hydroxy naphthalen-2-yl)-6-(4-hydroxy phenyl)-5,6-dihydropyrimidine-2(1H)-one.

Compound 2: 4-(4-Bromo-1-hydroxy naphthalen-2-yl)-6-(3, 4-hydroxy phenyl)-5,6-dihydropyrimidine-2(1H)-one.

Compound 3: 4-(4-Bromo-1-hydroxy naphthalen-2-yl)-6-(3-Hydroxy phenyl)-5,6-dihydropyrimidine-2(1H)-one.

Compound 4: 4-(4-Bromo-1-hydroxy naphthalen-2-yl)-6-(4-Hydroxy phenyl)-5,6-dihydropyrimidine-2(1H)-one.

SCHEME: -



Sr. no	Compound no	R1	R2	Molecular formula	Melting Point ^0C	% Yield	% Nitrogen		R.F Value
							Found	Calculated	
1	1	-OCH_3	-H	$C_{17}H_{17}N_2O_2Br$	259^{0}C	45%	6.64	6.61	0.55
2	2	-OCH_3	OCH_3	$C_{17}H_{19}N_2O_4Br$	225^{0}C	48%	6.21	6.74	0.59
3	3	-H	-OH	$C_{17}H_{15}N_2OBr$	228^{0}C	45%	6.89	6.84	0.55
4	4	-OH	-H	$C_{17}H_{15}N_2O_2Br$	269^{0}C	51%	5.84	5.85	0.58

Table 1. PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

SPECTRAL ANALYSIS: -

IR(νmax) (cm^{-1}): 1624 (C=O, str), 3346 (NH, str), 1568 (C=N), 1171 (C-O-C),758(monosubstituted Benzene

NMR (δ ppm): 1.3-1.8 (m, 2H, -CH_2 of pyrimidine), 10.30 (s, 1H, -OH),3.61 (s, 3H, -OH),2.51 (s, 3H, CH_3,)

ANTIMICROBIAL STUDIES: -

All above synthesized 4-(4-Bromo-1-hydroxy naphthalen-2-yl)-6-(4-hydroxy phenyl)-5,6-dihydropyrimidine-2(1H)-one have been studied for their antimicrobial activity against Escherichia coli, Proteus mirabilis, Staphylococcus aureus, Pseudomonas aeruginosa. The culture of each species was incubated at 37^{0}C and the zone of inhibition was measured after 24 hr. Results are tabulated in Table. Most of these compounds were found active

Sr. no	Compound Number	Antimicrobial Activity			
		E-coli	Proteus mirabilis	Staphylococcus aureus	Pseudomonas aeruginosa
1	1	17	18	15	10
2	2	18	10	16	14
3	3	16	13	14	15
4	4	15	14	12	13

Strongly active, range 15-19 Weakly active, range 7-10 mm, moderately active, range 11-14mm, Inactive, -

CONCLUSION: -

Thus, from above results it was observed that these heterocyclic compounds were found effective against Escherichia coli, Proteus mirabilis, Staphylococcus aureus, Pseudomonas aeruginosa. So those compounds can be easily be used for the treatment of diseases caused by test pathogens, only when they do not have toxic and other side effects.

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65

Efficient Synthesis of Salicylaldehyde-Based Schiff Bases Using Hydrothermal Sonication: A Green Approach

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This study presents a novel, efficient, and environmentally friendly procedure for the synthesis of a series of salicylaldehyde-based Schiff bases utilizing hydrothermal sonication. The procedure involves the condensation of salicylaldehyde with various aromatic amines in water under hydrothermal sonication conditions. Through meticulous selection of the solvent and reaction conditions, the final products are obtained in excellent yields in a single-step procedure. Comparative experiments under thermal conditions yielded lower yields and necessitated more laborious work-up processes. The hydrothermal sonication method demonstrates several advantages, including reduced reaction time, increased conversion, minimized waste production, and favorable yields. The synthesized compounds' structures were confirmed through the analysis of Infrared (IR), Proton Nuclear Magnetic Resonance (1HNMR and C13NMR), and Mass Spectra data. This research highlights the efficiency and environmental benefits of the hydrothermal sonication method in synthesizing salicylaldehyde-based Schiff bases.

Introduction

The increasing focus on the environmental impact of chemicals has prompted a drive towards cleaner and more eco-friendly synthetic processes. Stringent regulations are geared towards promoting sustainability by minimizing waste generation, eschewing the use of auxiliary substances such as organic solvents and additional reagents, and reducing energy demands. The utilization of water as the reaction medium is particularly advantageous in this context. Firstly, water is cost-effective, nonflammable, non-toxic, and poses minimal safety concerns [1, 3]. Secondly, its distinct physical and chemical properties often augment reactivity or selectivity, which may not be attainable with organic solvents. Lastly, employing water obviates the necessity to dry substrates or reagents prior to use, thereby diminishing or eliminating the consumption of drying agents, energy, and time.

The synthesis of Schiff bases traditionally involves the condensation of a primary amine with an aldehyde, often employing organic solvents such as methanol, tetrahydrofuran (THF), and 1,2-dichloroethane (DCE) [4]. Additionally, solvent-free methods utilizing hydrothermal sonication have been reported for the synthesis of Schiff bases [5]. A comparative analysis of these synthesis methods for simple Schiff bases revealed that hydrothermal sonication irradiation represents the most straightforward approach [6].

The use of Schiff base compounds as ligands is widespread due to their facile formation and diverse coordination chemistry, enabling their application as catalysts in various asymmetric reactions [7, 8]. Notably, Schiff base complexes derived from salicylaldehyde, 2-aminol, and 3,4-thiadiazole have been evaluated for their antibacterial activity against a range of bacterial strains, including Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa [9].

It was observed that the antibacterial efficacy of these Schiff bases was enhanced through chelation/complexation, demonstrating significant activity against the tested bacterial strains and presenting new avenues in combating antibiotic-resistant strains. In light of these discoveries, this manuscript presents the hydrothermal sonication-assisted synthesis of salicylaldehyde-based Schiff bases in aqueous media.

The synthesis of Schiff bases has been extensively documented in the literature [10–13]. However, the reported methods often entail a laborious process utilizing methanol or ethanol as solvents, leading to prolonged reaction times. Typically, the synthesis of Schiff bases through condensation reactions necessitates stringent conditions, including the use of a Dean Stark apparatus, catalysts, elevated temperatures, and extended reaction durations [14]. Notably, the significance of the fluorinated Schiff bases discussed in this manuscript is equally noteworthy. This significance stems from the influence of fluorine substitution on inter- and intramolecular forces, which affect ligand binding and introduce receptor subtype selectivity in biological systems [15, 16]. The breadth and universality of this synthetic process are demonstrated with respect to salicylaldehyde and various fluorinated amines.

In conclusion, we introduce a sustainable and effective approach for synthesizing Schiff bases in aqueous media, as illustrated in Scheme 1. The uncomplicated workup, convenient conditions, swift reaction kinetics, high yields, and reaction specificity collectively enhance the appeal of the current methodology.

Experimental

The purity of the compound was assessed using silica-gel-coated aluminum plates (Merck). Melting points were determined in open capillary tubes. Infrared (IR) spectra were recorded with KBr on a Perkin Elmer Spectrum RX-1 FTIR spectrophotometer. Proton nuclear magnetic resonance (1H-NMR) and carbon-13 nuclear magnetic resonance (13C-NMR) spectra were acquired on a Jeol JNM-ECX400P instrument operating at 400 MHz. Hydrothermal ultrasonication irradiations were conducted in a hydrothermal sonication synthesizer operating at 37 KHz using Hielscher instrument. All chemicals utilized were of analytical grade.

Conventional Method

Schiff bases were synthesized through the condensation of salicylaldehyde (0.005 mol) with various aromatic amines (a–f) (0.005 mol) in 10 mL of water. The reaction mixture was stirred at ambient temperature, and the progress of the reaction was monitored using thin-layer chromatography (TLC). Upon completion of the reaction, the product was isolated, filtered, dried, and subsequently recrystallized using methanol.

Hydrothermal ultra sonication method

The hydrothermal ultrasonication synthesis method involves subjecting the reactants to high-frequency ultrasound, generating intense sound waves that stimulate chemical reactions. In this sonochemical approach, the reactants are placed in a sonication vessel, exposed to high-frequency ultrasound, leading to localized heating, elevated pressures, and increased concentrations of reactive species, facilitating chemical transformations and yielding the desired Schiff base product.

A mixture comprising salicylaldehyde (0.005 mol) and substituted aromatic amines (2a–f) (0.005 mol) in 10 mL of water was introduced into a hydrothermal sonication tube. The contents underwent hydrothermal sonication irradiation at 37 KHz for a duration of 1 hour. The progress of the reaction was monitored via thin-layer chromatography (TLC). Upon completion

of the reaction, a solid product formed in the reaction mixture, which was subsequently filtered and recrystallized using methanol. The recrystallization process yielded the title compounds in the form of solid crystals.

Results and Discussion

A novel environmentally friendly method utilizing water as a solvent for the synthesis of Schiff bases has been successfully developed, as depicted in the schematic representation in Scheme 1. The optimization of %yield was investigated at various temperatures, revealing an optimal yield at 70 °C. Beyond this temperature, there was no significant change in yield, as summarized in Table 1. The results indicate that at 30 °C, the yield is 5.5%, and with an increase in temperature to 70 °C, the yield significantly improves to 53.5%. This tenfold increase in activity may be attributed to enhanced solubility, increased agitation, and a reduction in intermolecular distances. Consequently, the synthesis of other products (b–f) was carried out under the same reaction conditions, maintaining a temperature of 70 °C. The data suggests that the environmentally friendly method using water as a solvent, particularly at a temperature of 70 °C, significantly enhances the %yield for the synthesis of Schiff bases.

Table 1: Comparison of yield of Schiff base (a) at different temperatures under Hydrothermal ultra sonication.

Compound	Temperature (°C)	%Yield
3a	30	5.5
3a	35	7.5
3a	40	9.5
3a	45	10.0
3a	50	13.6
3a	55	19.5
3a	60	35.4
3a	65	46.2
3a	70	53.5
3a	75	55.1
3a	80	55.5

Reaction Conditions :- Sonication 37 KHz, Time 1 hr, solvent water, and aldehyde : base concentration 1:1 moles.

The impact of different compositions on %yield is detailed in Table 2. A variation in aldehyde and base composition resulted in an increase in %yield from 45.5 to 54.5. This observed increase is likely attributed to the stoichiometric composition of salicylaldehyde and substituted aromatic amines. The optimal %yield of 53.5 was achieved for a composition ratio of 1:1. Consequently, the same composition was adopted for the synthesis of other compounds (b-f). It's clear that the composition ratio of salicylaldehyde and substituted aromatic amines played a significant role in achieving the optimal %yield of 53.5. This information can be valuable for further experiments or scale up applications.

Table 2: Effect of composition of aldehyde and base for the formation of Schiff base (a)

Composition		%Yield
Aldehyde (mole)	Base (mole)	
1	0.75	45.5

1	1.00	53.5
1	1.25	54.1
1	1.50	54.5

Reaction Conditions :- Temperature 70 °C, sonication 37 KHz, Time 1 hr, solvent water.
The comparative result analysis of the hydrothermal ultrasonication method is presented in Table 3. The results obtained with this method were significantly higher, by almost 50%, compared to the conventional hydrothermal method. This suggests that the hydrothermal ultrasonication method, by enhancing the contact time of reactants, leads to a higher %yield. Consequently, this highlights the advantageous nature of the hydrothermal ultrasonication synthesis for the preparation of various Schiff bases. The data indicates that the hydrothermal ultrasonication method is a more effective approach for the synthesis of Schiff bases, resulting in a substantial increase in %yield compared to the conventional hydrothermal method. This insight could be valuable for researchers and practitioners in the field of chemical synthesis.

Table 3: Comparative study of hydrothermal ultra sonication and conventional method.

Compound	% Yield	
	Hydrothermal ultra sonication	Conventional
a	53.5	21.0
b	85.6	37.9
c	81.3	37.5
d	80.4	37.5
e	78.4	39.8
f	80.5	32.5

Reaction Conditions :- Temperature 70 °C, sonication 37 KHz, Time 1 hr, solvent water and aldehyde : base concentration 1:1 moles.

Product Characterization Data

(a) (E)-2-(((2,4-dimethylphenyl)imino)methyl)phenol, colorless solid, M.P. 91- 93°C, IR (KBr, cm^{-1}): 2927.60, 2700, 1615.96, 1490.71, 1282.72, 1144.23, 1HNMR (400 MHz, $CDCl_3$) (δ ppm): 8.87 (1CH, s), 7.66 (1H, d), 7.08 (2H, d), 70.2 (1H, s), 7.01 (1H, m), 2.34 (6H, m). 13C-NMR ($CDCl_3$) (δ ppm): 161.1, 160.0, 132.4, 132.1, 121.4, 120.5, 117.8, 148.1, 132.2, 128.7, 128.7, 127.3, 122.1, 21.6, 18.6, . M/S: 226.12 (M + 1).

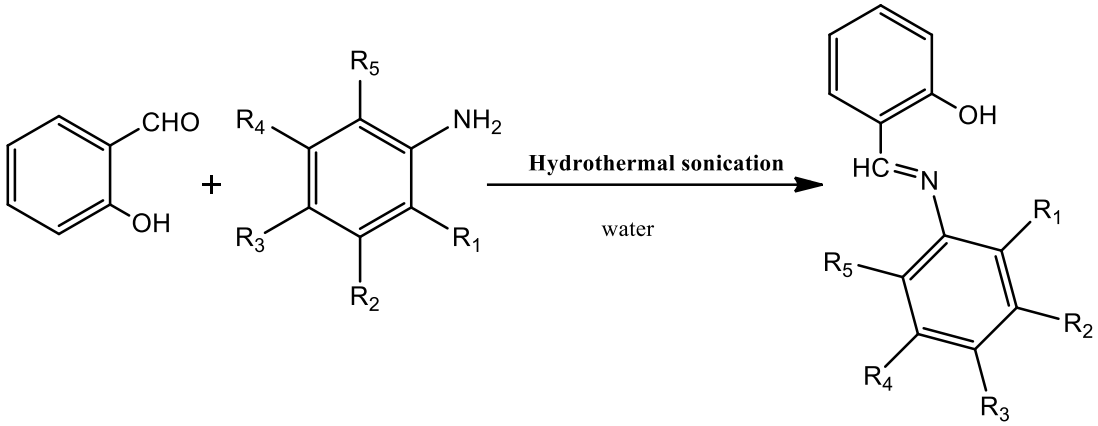
(b) 2-[(4-Chloro-phenylimino)-methyl]-phenol [10]. Yellow solid, M.p. 95–98°C, IR (KBr, cm^{-1}): 2920.94, 1620.86, 1487.51, 1278.31, 1134.17, 1HNMR (400 MHz, $CDCl_3$): δ ppm = 13.06 (1CH, s), 8.88 (1H, s), 7.67 (2H, d), 7.57 (1H, m), 7.49 (1H, t), 6.70 (3H, m). 13C-NMR ($CDCl_3$) (δ ppm): 159.21, 164.71, 163.28, 158.72, 138.09, 134.02, 133.01, 122.08, 120.72, 119.02, 117.41, 112.01, 105.05. M/S: 234.8 (M + 1).

(c) 2-[(4-Chloro-phenylimino)-methyl]-phenol [11]. Golden solid, M.p. 70–73°C, IR (KBr, cm^{-1}): 2950.53, 1617.09, 1474.16, 1272.73, 841.22, 1HNMR (400 MHz, $CDCl_3$): = δ 12.92 (1 H, s), 8.41 (1 H, s), 7.64 (2 H, d), 7.51 (2 H, d), 7.52 (2 H, dd), 7.34 (1 H, d), 7.02 (1 H, t). 13C-NMR ($CDCl_3$) (δ ppm): 163.07, 162.08, 148.01, 134.01, 133.32, 132.27, 132.18, 129.11, 123.03, 120.07, 119.01, 118.10. M/S: 232.84 (M+ 1).

(d) 2-[(2,3,4,5-Tetrafluoro-phenylimino)-methyl]-phenol [12]. Greenish solid, M.p. 141–143°C, IR (KBr, cm^{-1}): 2931.04,1618.71, 1467.17, 1040.21, 775.99. 1HNMR (400 MHz, $CDCl_3$): δppm = (1H, s), 8.41 (1H, s), 7.34 (2H, dd), 7.16 (1H, d), 6.91 (2H, m). 13C-NMR ($CDCl_3$) (δppm): 164.19, 159.30, 139.25, 134.99, 132.55, 131.72, 129.95, 129.66, 117.83, 117.49, 116.58, 115.61, 101.07. M/S: 270.27 (M + 1).

(e) 2-[(4-Bromo-phenylimino)-methyl]-phenol [11, 12]. Greenish solid, M.p. 97–99°C, IR (KBr, cm^{-1}): 2911.15, 1616.74, 1480.31, 1271.05, 837.16, 763.41, 1HNMR (400 MHz, $CDCl_3$): δppm = (1H, s), 8.55 (1H, s), 7.51 (2H, d), 7.49 (2H, m), 7.11 (2H, d), 7.12 (1H, d), 6.97 (1H, t). 13C-NMR ($CDCl_3$) (δppm): 161.99, 161.23, 147.67, 133.48, 132.44, 132.79, 122.19, 120.34, 119.41, 119.50, 117.62. M/S: 276.1 (M + 1).

(f) 2-[(4-Fluoro-phenylimino)-methyl]-phenol [13]. Yellow solid, M.p. 71–73°C, IR (KBr, cm^{-1}): 2927.88, 1614.71, 1494.00, 1260.05, 830.04, 1HNMR (400 MHz, $CDCl_3$): δ ppm= 13.01 (1H, s), 8.58 (1H, s), 7.37 (2H, m), 7.26 (2H, m), 7.12 (2H, m), 7.03 (1H, d), 6.94 (1H, t). 13C-NMR ($CDCl_3$) δppm= 163.40, 161.08, 159.17, 142.01, 131.08, 128.45, 121.02.



a) :- $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$, $R_4 = H$, $R_5 = H$
b) :- $R_1 = F$, $R_2 = H$, $R_3 = F$, $R_4 = H$, $R_5 = H$
c) :- $R_1 = H$, $R_2 = H$, $R_3 = Cl$, $R_4 = H$, $R_5 = H$
d) :- $R_1 = F$, $R_2 = F$, $R_3 = F$, $R_4 = F$, $R_5 = H$
e) :- $R_1 = H$, $R_2 = H$, $R_3 = Br$, $R_4 = H$, $R_5 = H$
f) :- $R_1 = H$, $R_2 = H$, $R_3 = F$, $R_4 = H$, $R_5 = H$

Conclusions

In summary, the synthesis of Schiff bases through condensation reactions using both conventional hydrothermal and hydrothermal ultrasonication methods was investigated, with the latter proving to be the more efficient approach. The tenfold increase in activity observed with an increase in temperature from 30 to 70 °C can be attributed to enhanced solubility, increased agitation, and a reduction in intermolecular distances. The highest %yield, reaching 53.5%, was achieved with a composition of salicylaldehyde and the base at a temperature of 70 °C. The optimal composition of salicylaldehyde and substituted aromatic amines was found to be 1:1 for maximum %yield. Subsequently, the synthesis of other products (b–f) was carried out with a composition ratio of 1:1, maintaining a temperature of 70 °C. The data obtained indicates that the hydrothermal ultrasonication method is a more effective approach for the synthesis of Schiff bases, resulting in a substantial increase in %yield compared to the

conventional hydrothermal method. This insight holds significance for researchers and practitioners in the field of chemical synthesis.

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66

Viscometric Technique for Evaluation of 1-Phenyl-3-[4-(2-Ethylimino-4-T-Butylimino-1,3,5-Dithiazino)Amino-Phenyl]Prop-2-Ene-1-One in Ethanol-Water Mixture

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ABSTRACT

The evaluation of density and viscometric study of 1-phenyl-3-[4-(2-ethylimino-4-t-butylimino-1,3,5-dithiazino)aminophenyl]prop-2-ene-1-one was recently carried out in our laboratory. In this research work evaluation done at different temperatures by keeping the constant concentration. The experimental data determine the effect of dilution of the solvent and the solute-solvent interaction of drug in current times.

KEYWORDS

Solute-solvent interaction, Viscometric study, 1,3,5-Dithiazino etc.

INTRODUCTION

The chalcones moiety base heterocyclic compounds are very widely distributed in nature. The nitrogen and sulphur containing heterocyclic compounds are very essential to living organisms. In biochemical, agricultural, pharmaceutical, medicinal, and industrial and drug sciences (Solanki A. and Thakur I, 2007) (Saleem F, 2008) viscosity measurements play a crucial role. Liquid have one of the important physical property is viscosity. Due to the shearing effect in the liquid which is the movement of liquid layers over each other hence liquids are viscous in nature (Bhat B.A., 2008). For aqueous and in non-aqueous solution have solute-solute and solute-solvent interaction. This important information provided by measurements of viscometric parameter. Drug behavior like absorption, transmission and its effect will directly relate to its viscosity measurements and solvent interactions in the human framework (Vibhute Y.B. and Basser M.A., 2008)

Literature review that chalcone derivatives exhibit diverse pharmacological and biochemical activities such as antimicrobial and cytotoxic agents, antiviral, anti-inflammatory, anestetics, mydriatics. Heterocyclic molecule having 1,3,5-dithiazino nucleus is widely used in medicinal, biochemical, biotechnological and pharmaceutical sciences (Solanki A. and Thakur I, 2007) (Saleem F, 2008) (Bhat B.A., 2008). These compounds showed anti-helminthic, antifungal, antiviral, antibacterial and anti-tuberculostatic properties Vibhute Y.B. and Basser M.A., 2008). Dithiazines are found to be effective on treatment of cancer (Wan Z.Y., 2005). All these facts consideration a topic of great interest to carry out the viscometric measurements of 1-phenyl-3-[4-(2-ethylimino-4-t-butylimino-1,3,5-dithiazino)aminophenyl]prop-2-ene-1-one by varying temperatures (Jakhar A. and Makrand J.K.,2010) Such kind of study will be helpful to drug effectiveness (Zhang L.X., Zhang A.J., 2003) (Solanki A. and Thakur I, 2007) (Saleem F, 2008).

EXPERIMENTAL

For all type of analysis double distilled water and A.R. grade chemicals were used throughout the evaluation. For compound weight was used Mechaniki Zektady Precyzyjnej Gdansk balance [Poland make (±0.001gm)]. For measurement of viscosity of liquid was used Ostwald's viscometer. It was kept in Elite themostatics water bath and temperature variation was maintained at 29^0C (±0.1) for each measurement. For densities determination bicapillary with a 1 mm internal diameter was used. Viscometer and water bath required sufficient time for maintaining thermal equilibrium.

In this research work viscometric study of 1-phenyl-3-[4-(2-ethylimino-4-t-butylimino-1,3,5-dithiazino)aminophenyl]prop-2-ene-1-one at 0.1M concentration in 60% ethanol-water system separately at varying temperatures. Freshly prepared solutions were used throughout the evaluation. As per the literature given viscometric readings were taken.

OBSERVATIONS AND CALCULATIONS

Molecular interactions in terms of β-coefficient of solute is figured with the help of data obtained in our work. The results obtained are stated in **Table No. 1**. According to Jone's-Dole equation, $(\eta r-1)/\sqrt{C} = A+B\sqrt{C}$ at different temperatures keeping the concentration 0.1 M. A and β-coefficient values calculated are enlisted in **Table No.2.**

TABLE No.1
VISCOSITY MEASUREMENTS AT CONSTANT CONCENTRATIONS AND DETERMINATION OF RELATIVE AND SPECIFIC VISCOSITIES AT DIFFERENT TEMPERATURES AT 0.1M

MEDIUM - 60% ETHANOL-WATER							
Conc.	**Temp. (°C)**	**√C**	**Time (sec.)**	**Density ρx10^3 (kg.cm^{-3})**	**$\acute{\eta}_r$**	**$\acute{\eta}_{sp}=\acute{\eta}_r-1$**	**$(\acute{\eta}_r-1)/\sqrt{C}$ (pa-s)**
0.1 M	22	0.314	58	1.0913	0.069341	-0.930659	-2.9638
	24	0.314	51	1.0893	0.067329	-0.932671	-2.9702
	28	0.314	47	1.0676	0.05920	-0.9408	-2.9961
	30	0.314	32	1.0565	0.06453	-0.93547	-2.9792

TABLE No.– 2
A and β Co-Efficient Values from Graphs for 60%.
FOR 1-PHENYL-3-[4-(2-ETHYLIMINO-4-t-BUTYLIMINO-1,3,5-DITHIAZINO)AMINO- PHENYL]PROP-2-ENE-1-ONE

W-E Mixture(%)	Temp° C	Mean "A"	β (Slope "m")
60	24	-2.9702	0.0073

RESULT AND DISCUSSION

The relative viscosity was determined by using following formula

η_r = Ds x ts / Dw x tw.

While Jone's-Doles equation was used for the analysis of relative viscosities,

$(\eta r-1)/\sqrt{C} = A+B\sqrt{C}$

Where,

A = Falkenhagen coefficient

B = Jones-Dole coefficient
C = concentration of solutions
Solute-solute interaction was measures by using Falkenhagen coefficient (A) while solute-solvent interaction was measures by using Jones-Dole coefficient (B).
The graph are plotted in between $(\eta r-1)/\sqrt{C}$ versus $\sqrt{C}$. The graph for each system gave linear straight line gave value of β-coefficient.

CONCLUSIONS

In the current work monitor that the density and relative viscosity decreases with increase in temperature. This is supported by the information that as the temperature increases the solute-solvent interaction increases due to which solvation effect increases. Pharmacodynamics and pharmacokinetics study of drug is useful investigation and informative for society.

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67

An Overview on Green Chemistry

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ABSTRACT
The present review work focuses on the importance and economic development of green chemistry. It is new branch in chemistry dealing with reduction of harmful and toxic chemicals in the synthesis and replacing it with ecofriendly methods. The principle of green chemistry with various benefits have been discussed to understand the basic requirement for replacement of conventional synthetic method with green chemistry synthesis. To describe it the synthetic approach for the synthesis of acetanilide has been discussed and compared.

KEYWORDS: Green Chemistry, Ecofriendly, Conventional, Acetanilide.

1. INTRODUCTION

The accelerated progress in science and technology now a days has led to economic development in world, but such economic development also cause environmental degradation which is manifested by climate change, the issue of ozone holes and accumulation of non-destructive organic pollutant in all parts of biospheres.

So the present situation required the solution to balance the use of natural resources and environmental conservation. From last two decades awareness for environmental protection has increased by using the concept of "Green Chemistry". The new laws and regulations have a Aim to protect the ecosystem from harmful chemicals and develop new compounds by the approach of Green chemistry which are less dangerous to human health and the environment.[1].

Green chemistry is new branch of chemistry involves pulling together tools and techniques that helps to chemical engineers in research related to the creation of chemical product and processes that reduce or eliminate the use of harmful chemicals as well as reducing harmful and toxic products for the development of more eco-friendly and efficient product with less wastage. Green chemistry is now going to become an essential tool in the field of synthetic chemistry [2,3].

1.1.Definition of Green Chemistry: According to environmental protection agency, green chemistry is defined as a chemistry that designs chemical products and processes that are harmless to the environment. Chemical products should be made in such a manner that they do not remain in the environment at the end of their application and broken down into components that are harmless to environment.[4]

1.2.History: The term green chemistry was first given by Poul .T. Anastas in 1991 in special program launched by the US environmental Protection Agency (EPA) to implement sustainable development in chemistry ,chemical technology by industry ,academia and government. In 1995 the annual US presidential green chemistry challenge was announced. In 1996 the working party on green chemistry was created, acting within the framework of International Union of Pure and Applied Chemistry. The first book and journals on the subject of green chemistry were introduced in 1990 by the royal society of chemistry. Green chemistry includes a new approach to the synthesis, processing and

application of chemical substances in such a manner to reduce scourge to health and environment like:

- Clean chemistry
- Atom Economy
- Environment begin chemistry [5-11]
- Clean Chemistry
- Atom Economy

Twelve principles of Green chemistry have been developed by Poul Anastas, speaks about the reduction of dangerous or harmful substances from the synthesis, production and application of chemical products. When designing a green chemistry process it is impossible to meet the requirements of all twelve principles of the process at the same time, but it attempts to apply as many principles during certain stages of synthesis.[12,13]

1.3. Principles of Green Chemistry

1.3.1. Pollution Prevention: It is to prevent waste and to treat and clean up waste after it has been created.

1.3.2. Atom Economy: It should be designed to maximize the incorporation of all materials used in process into the final product.

1.3.3. Less Hazardous Chemical Synthesis: The synthetic method should be designed to use and generate substances that process little or no toxicity to human health and the environment.

1.3.4. Designing Safer Chemicals: Chemical product should be designed to affect their desired function while minimizing toxicity.

1.3.5. Safer Solvents and Auxiliaries: The use of auxiliary substances should be made unnecessary wherever possible.

1.3.6. Design for Energy Efficiency: energy requirements of chemical processes should be recognized at low temperature and pressure.

1.3.7. Use of Renewable Feedstock's: A raw material of feedstock should be renewable.

1.3.8. Reduce Derivatives: The unnecessary derivatization like use of blocking groups, protection, deprotection should be avoided whenever impossible.

1.3.9. Catalysis: The catalytic reagents are superior stoichiometric reagents.

1.3.10. Design for Degradation: The chemical products should be designed so that at the end of their function they breakdown into harmless degradation products and do not persist in the environment.

1.3.11. Real-time analysis for Pollution Prevention: Analytical methodologies need to be further developed to allow for real-time, in process monitoring and control prior to the formation of hazardous substances.

1.3.12. Inherently Safer Chemistry for Accident Prevent: The substances used in the chemical process should be chosen to minimize the potential for chemical accidents, explosion and fires. This principle can motivate chemistry at all levels like research, education and public perception. [14]

1.4. Benefits of Green Chemistry

Benefits for health

- ✓ Cleaner air- less release of hazardous chemicals to air leading to less damage to lungs.
- ✓ Cleaner water- less release of hazardous chemicals waste to water leading to cleaner drinking.
- ✓ Increase safety water for workers in chemical industry, less use of toxic material, less potential for accident

- **Benefits for environment**
  - ✓ Plants and animals suffer less harm from toxic chemicals in environment
  - ✓ Lower potential for Global warming, ozone depletion and smog formation.
- **Economy**
  - ✓ Better performance so that less product is needed to achieve the same function.

REVIEW LITERATURE

2.1. Green chemistry aims to reduce or even eliminates the production of any harmful bi-products and maximizing the desired product without compromising with the environment. The three key developments in green chemistry include use of super critical carbon di oxide as green solvent, aqueous hydrogen peroxide as an oxidizing agent and use of hydrogen in asymmetric synthesis. It also focuses on replacing traditional methods of heating with that of modern methods of heating like microwave radiations so that carbon footprint should be reduces as low as possible.[15]

2.2. The work focuses to reduce the chemical wastage by applying the concept of green chemistry. Few derivative of acetanilide were synthesized by conventional method as well as by green chemistry method. In conventional method there was wastage of chemicals by the formation of acetic acid molecule but by green synthesis method the formation of byproducts was avoided and the atom economy was calculated on the basis of molecular weight of desired product and it was found to be in the range of 72 to 82% which signify the utility of green synthesis method.[16]

2.3. Due to technology development the quality of life on earth became much better but harmful effect of chemistry also became pronounced main among them being the pollution of land, water and atmosphere. This is caused mainly due to the use of harmful reactants and effect of by-product of chemical industries, which are being discharge into air, rivers and the land, but by applying the concept of green chemistry these all problems can be reduced.[17]

2.4. Green chemistry is a term that refers to the production of chemical products and processes that reduce the use of and production of harmful substances[18]

The green chemistry revolution provides the various numbers of challenges to those who practice chemistry in industry, education and research. It is the modern science of chemistry deals with the application of environment friendly chemical compound in the various area of our life such as industries. The chemical industries supply us a huge variety of essential product, from plastic to pharmaceuticals, these industries has a potential to damage our environment, so green chemistry serves to promote the design and efficient use of chemicals and chemical processes [19]

3. EXPERIMENTATION

The synthesis of acetanilide by green chemistry has various disadvantages as there is a lot of wastage of acetic acid molecule, which can be minimized by green chemistry.

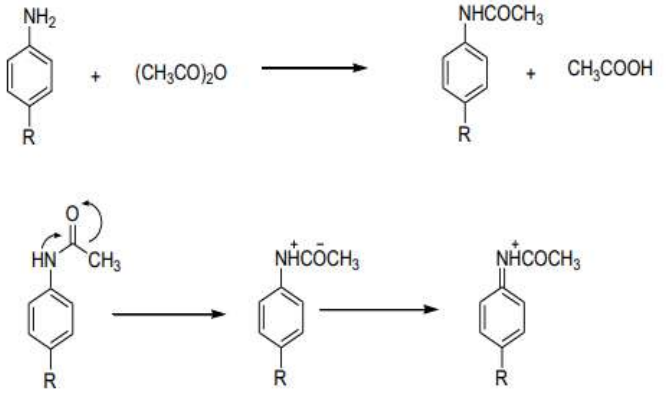
3.1. Synthesis of compounds by conventional method

- In a 250 ml beaker containing 125 ml of water, 4.6 ml of conc. Hydrochloric acid and 5.1
- In a 250 ml beaker containing 125 ml of water, 4.6 ml of conc. Hydrochloric acid and 5.1 g of aniline / substituted anilines were introduced.
- Stirred until all the anilines passes completely into solution.
- To the resulting solution, 6.9 g (6.4ml) of redistilled acetic anhydride was added and stirred until it was dissolved.

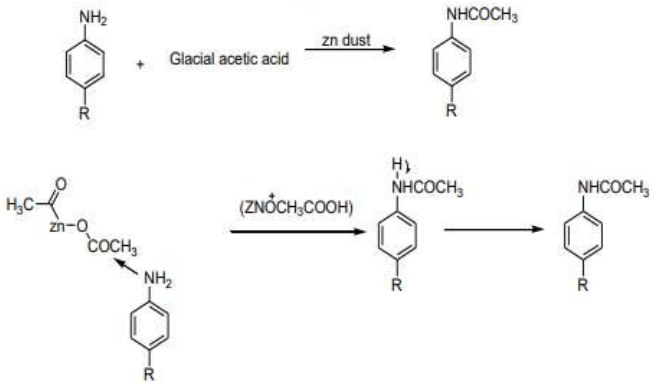
- Poured immediately in a solution of 3.8 g of crystalline sodium acetate in 25 ml of water.
- Stirred vigorously and cooled in ice. Filtered the acetanilide and substituted acetanilide with suction, washed with 10 ml water, drained well and dried upon filter paper. The crude products were recrystallized from boiling water and methylated spirit.
- Non green component: Acetic anhydride leaves one molecule of acetic acid unused.
- Poured immediately in a solution of 3.8 g of crystalline sodium acetate in 25 ml of water.
- Stirred vigorously and cooled in ice. Filtered the acetanilide and substituted acetanilide

3.2. Synthesis of compounds by green chemistry method

- A mixture of aniline / substituted anilines (3.3g) and zinc dust (0.16g) in acetic acid
- A mixture of aniline / substituted anilines (3.3g) and zinc dust (0.16g) in acetic acid (10ml) in 100 ml round bottom flask was heated over a gentle flame using water condenser.
- Heating was continued for about 45 min., the reaction mixture was then carefully poured in cold water (33ml) in 250ml beaker with vigorous stirring.
- The shining crystals of product were separated slowly. After 15 min, crystals were collected by filtration. The solid crystals were washed over the Buchner funnel with water and product was dried and crystallized in boiling water.
- Green context: Minimize waste by-products, avoids use of acetic anhydride
- Benefits for health
- Cleaner air-less release of hazardous chemicals to air leading to less damage to lungs.
- Cleaner water-less release of hazardous chemical wastes to water leading to cleaner



Synthesis and mechanism by conventional method



Synthesis and mechanism by green chemistry method

4. CONCLUSION

This review article will definitely help to understand the importance of green chemistry, conventional methods can be replaced easily by the methods which utilize non toxic and environment friendly techniques for the synthesis of same. One of such approach has been discussed for the synthesis of acetanilide. The approach will definitely help in the synthesis by keeping the environment safe. which is basic requirement in today's pharmaceutical industries. The approach will help to avoid the utilization of the toxic chemicals leading to various hazards in the industry. These

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68

3D Printing Technology for development of Transdermal Drug Delivery Systems

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Abstract:
The innovative approach of three-dimensional printing enables the on-demand production of transdermal drug delivery systems. This technology, already applied in dentistry, orthopedics, and pharmaceuticals, particularly stands out in the latter field. It facilitates the printing of medical devices and diverse formulations of active pharmaceutical ingredients, featuring controlled-release characteristics and varied geometries. This study provides an overview of these pharmaceutical applications, focusing on the 3D printing of transdermal patches. The discussion encompasses different printing technologies and material systems known for their customization capabilities, generating intricate geometries with precise characteristics crucial for transdermal systems, thereby enhancing bioavailability. The study includes case studies, explores advantages and limitations of the technology, and forecasts industry growth, projecting a value exceeding USD 8 Billion by 2025. Despite this potential, the conservative nature of the pharmaceutical industry leans toward cost-effective methods for large-scale production. Nevertheless, 3D printing has the potential to revolutionize the current 'one size fits all' manufacturing approach, becoming an integral part of the drug development timeline.

Keywords: 3D Printing, Inkjet printing, Microneedles, Patches, Transdermal delivery, Pharmaceutics

1. Introduction

The historical application of therapeutic substances, including herbal ointments and various drugs (such as scopolamine, estradiol, fentanyl, rivastigmine), on the human skin serves both medical and cosmetic purposes. Over the past decades, the skin has proven to be an accessible surface for drug administration, making systematic therapy through percutaneous drug absorption feasible (Prausnitz and Langer, 2008; Alkilani et al., 2015; Pastore et al., 2015). The transdermal route emerges as an attractive alternative to traditional methods like oral administration or hypodermic injections. Oral administration may face issues of partial drug absorption, complications related to gastrointestinal metabolism, and slow onset, making it impractical for emergency cases. Hypodermic injections, while effective, are invasive, pose infection risks, require skilled administration, and generate medical waste (Awodele et al., 2016).

Contrarily, transdermal systems offer advantages such as bypassing metabolic systems, ensuring higher bioavailability, and promoting sustained and controlled drug release. Additionally, transdermal drug delivery (TDD) holds promise for vaccinations due to the abundance of dendritic cells in the skin. This patient-friendly approach is noninvasive, contributing to psychological well-being, and provides independence as it doesn't require professional care for repositioning, removal, or replacement.

However, TDD faces limitations, primarily stemming from the skin barrier's nature. The Stratum Corneum, the outermost skin layer, acts as a significant barrier due to its density and low hydration (15–20%). Overcoming this impermeable barrier has been the focus of TDD research, presenting both challenges and opportunities for future progress.

In the current global trend towards personalized patient care, traditional mass-production methods of drug delivery systems are being questioned for their ability to tailor dosages cost-effectively. New technologies, particularly Additive Manufacturing (AM), such as 3D printing, are investigated for their potential in pharmaceutical technology. Initially introduced in the 1980s, 3D printing has gained attention across various industries, contributing to the production of complex structures beyond the capabilities of conventional techniques.

The application of 3D printing in pharmaceuticals is relatively recent, aiming to produce targeted-release and customized drug delivery systems (Goole and Amighi, 2016). In the field of TDD, although studies are limited, they demonstrate the transformative potential of 3D printing. This review explores the existing research on 2D and 3D printing as direct or indirect fabrication methods for TDD systems. The materials and drugs associated with 3D printing in TDD systems are also examined in this context.

2. 3D printing techniques for optimized Transdermal Drug Delivery Systems

Additive Manufacturing (AM), commonly referred to as 3D printing or Solid Freeform Fabrication (SFF), encompasses various techniques that utilize a virtual Computer Aided Design (CAD) model to construct a physical object by depositing consecutive layers. Introduced in the 1980s, 3D printing has revolutionized industrial and scientific sectors, offering fast and precise production of intricate structures beyond the capabilities of traditional methods. The medical field quickly recognized the transformative potential of 3D printing, leading to the creation of customized implants, prosthetics, and ongoing investigations into live tissue printing (Chia and Wu, 2015).

The application of 3D printing in drug delivery has recently gained attention, with the FDA approval of Spritam, the first 3D printed oral administration tablet. This has given rise to the term 'pharmacoprinting' (Prasad and Smyth, 2015; Jacob et al., 2014; Goyanes et al., 2015; Di Prima et al., 2016). While its impact on oral drug delivery is well-established, 3D printing's potential in transdermal drug delivery (TDD) is currently under exploration, with a growing body of relevant studies.

2.1. Inkjet Printing

Inkjet printing, involving the controlled deposition of small droplets, has seen successful applications in medicine but is yet to be extensively explored for TDD. Studies have used inkjet printing for coating microneedles with various agents, demonstrating its potential for controlled and selective deposition on suitable substrates (Boehm et al., 2011, 2013, 2014; Ross et al., 2015; Uddin et al., 2015). While its application for building complex three-dimensional TDD structures remains unexplored, inkjet printing's high resolution and selective deposition make it promising for microneedle coating, enabling personalized dosages with high reproducibility.

2.2. Photopolymerization-based Technologies

A significant group of 3D printing technologies relies on selective polymerization of photo-sensitive polymers through laser emissions or light projections. Techniques like Stereolithography (SLA) and Digital Light Processing (DLP) enable layer-wise polymerization of UV-sensitive polymers. These technologies offer versatility in geometric complexity and resolution, making them suitable for TDD applications. Studies have utilized micro-stereolithography (DLP) to create microneedle arrays indirectly, contributing to the customization of therapeutic approaches (Boehm et al., 2014, 2011, 2012). Photopolymerization-based 3D printing has proven applications in fabricating TDD systems, offering high resolution and flexibility.

2.3. Fused Deposition Modelling (FDM)

Fused Deposition Modelling (FDM), based on the melt-extrusion process, is a versatile 3D printing technique with potential applications in TDD. While FDM's limitations in resolution and sensitivity to process parameters are acknowledged, its ability to produce structures through extrusion without solvents makes it a compelling choice for certain pharmaceutical applications. The combination of FDM with hot-melt extrusion (HME) processes holds promise for producing drug/polymer blends for cost-effective TDD system fabrication.

3. Materials:

In the contemporary landscape, 3D printing technologies possess the capability to manipulate a diverse array of materials, ranging from ceramics and metals to polymers. The categorization of these techniques implies that the choice of a specific technology inherently limits the materials compatible with the corresponding printing apparatus. For instance, SLA or DLP printers exclusively handle photo-cured polymers, while FDM printers utilize thermoplastic filaments. This limitation poses challenges for the widespread adoption of 3D printing as a direct manufacturing technique for Transdermal Drug Delivery (TDD) systems, as the material must meet specific criteria for integration into such systems. (Sharma et al.2011) Essential parameters include stability, biodegradability without toxic by-products, mechanical strength, and non-reactivity with the drug. Material biocompatibility is a critical consideration, as evidenced by studies involving Gantrez, a biocompatible copolymer used in TDD applications. While there's evidence of manufacturing Gantrez biocompatible microneedles using 3D printed molds, the multi-step nature of this approach may hinder mass production scalability. (Boehm et al., 2014, 2011, 2012, Donnelly et al., 2012).

Numerous polymers with biomedical and pharmaceutical applications show promise for integration into 3D printed TDD systems. Polyvinyl alcohol (PVA) and poly lactic acid (PLA) are examples. However, challenges exist, such as PVA's limited biodegradability and PLA's slow degradation rates and poor mechanical properties when employed in FDM technology. Biopolymers, like chitosan and collagen, exhibit favorable attributes for TDD. Bioprinting advancements further expand the possibilities. Yet, ongoing research on materials remains vital for the evolving field of 3D printed TDD. (Economidou et al. 2018)

4. 3D Printed Transdermal Drug Delivery Systems- Future Challenges and Expected Impact:

Transdermal Drug Delivery (TDD) systems, facilitated by 3D printing, hold potential as a user-friendly, personalized pharmaceutical therapy. The layer-by-layer fabrication inherent in 3D printing aligns well with TDD requirements. This technology enables the creation of systems with varying drug concentrations across layers, catering to individual needs. Customization possibilities enhance TDD efficiency, addressing factors like skin hydration and thickness variations among patients. In vaccination, microneedles offer promise, particularly in regions facing challenges with traditional administration methods. 3D printing's role in reducing costs and providing needle-free solutions is crucial for global health initiatives. However, challenges such as limited biomaterial options, dosing constraints, and drug degradation characteristics need resolution. The development of 3D printable materials and improvements in existing technologies could drive the evolution of TDD systems. (Economidou et al. 2018)

5. Regulatory Considerations:

For the commercialization of 3D printed TDD systems, adherence to regulatory requirements is essential. Despite the FDA's approval of the first 3D printed oral tablet, TDD systems face unique regulatory challenges. Microneedle patches, viewed as medical devices, must adhere to Good Manufacturing Practice (cGMP) guidelines. The FDA emphasizes technical

considerations, including the impact of printing parameters, in-situ quality control, design validation, sterilization, and post-process cleaning. A 2017 guidance document provides recommendations for 3D printed medical devices, addressing issues like patient-matched devices and data protection. Sterilization, a regulatory requirement, presents challenges for microneedles. Future success depends on addressing material limitations, improving technology, and establishing specific regulatory frameworks for 3D printed TDD systems. (Economidou et al. 2018)

6. Conclusion:

Since its inception, 3D printing has revolutionized fabrication methods, with potential applications in medicine and pharmaceutics. Despite being in the early stages, advancements in 3D printed Transdermal Drug Delivery (TDD) systems show promise. Inkjet printing, photopolymerization-based technologies, and FDM have been explored, with inkjet printing successfully depositing films on microneedle surfaces and commercializing 3D inkjet printed microneedles. The integration of elaborate microneedle array systems with precise 3D printing techniques has the potential to reshape modern drug administration. Overcoming engineering, chemistry, and material challenges through interdisciplinary research is crucial. Regulatory considerations, addressed by the FDA, are imperative to ensure the safety and effectiveness of 3D printed TDD systems. Success hinges on resolving material limitations, advancing technology, and establishing specific regulatory frameworks.

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69

In-silico Prediction of Phytoconstituents from *Hymenodictyon excelsum* for Antimalarial Activity Targeting Hypoxanthine-guanine phosphoribosyltransferase (HPRT1)

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ABSTRACT

Objective Malaria is referred as a disease cause by parasite. The parasite spread to humans through the infected mosquito bite. People who infected by malaria feel very sick with high fever and chills. Natural products and their active principles as sources for new drug discovery and treatment of diseases have attracted considerable attention of researchers. Compounds found in medicinal plants have been the source of many conventional medications. *In-silico* testing of *Hymenodictyon excelsum* phytoconstituents on hypoxanthine-guanine phosphoribosylt ransferase for antimalarial efficacy was a part of our investigation.

Methods Utilizing Discovery studio, molecular docking is done to assess the pattern of interaction between the phytoconstituents from the *Hymenodictyon excelsum* plant and the crystal structure of the malarial proteins (PDB ID: 4RAC). Later, SwissADME and pkCSM were used to screen for toxicity as well as the pharmacokinetic profile. Further, interaction between proteins by STRING network analysis and bioactivity score analysis using molinspiration tool were also evaluated.

Results The docked results suggest that nordamnacanthal (−8.9 kcal/mol), rubiadin (−8.2 kcal/mol) and lucidin (− 8.1 kcal/mol) for 4RAC macromolecule has best binding towards antimalarial activity as compared to the standard (artemisinin) for 4RAC is -7.5 kcal/mol and. Furthermore, pharmacokinetics and toxicity parameters were within acceptable limits according to ADMET studies.

Conclusions Targeting hypoxanthine-guanine phosphoribosyl transferase against malaria by phytoconstituents from *Hymenodictyon excelsum* can serveas a rational approach for designing future antimalarial drugs.

1. INTRODUCTION

About 30 species of flowering plants belong to the genus *Hymenodictyon*, which is part of the Rubiaceae family. The generic name is a combination of the Greek words for membrane and net, hymen and diktyon. It alludes to the wing that envelops every seed. The members in this genus have serrated leaves grouped in opposition, small, clustered blooms, and many seeds capsules. The genus includes widely varying trees and shrubs the majority of them in tropical and subtropical regions of Asia and Africa.[1]

Hymenodictyon excelsum Roxb. Wall. *syn H. orixense* Roxb Mobb. belonging to family Rubiaceae, also known as Bhorsal, Kukurkat, Bhaulan, Bauranga, Pottaka, Kusan, and Kadambu (India), Lala (Thailand), and Kuthan (Burma) is a medium to a tall, deciduous tree that typically grows to a height of 10 to 12 metres grey-brown with hints of brown, straight cylindrical bole, rounded crown green, glabrous leaves that are rectangular, ovate, or elliptic in shape, greenish-white, fragrant flowers, and ellipsoid capsules that contain flying seeds Bark

is 10-20 cm long and mostly ruffled, thick, softish scales that exfoliate in irregular shapes. Stipules are approximately 15 mm length, linear to lanceolate to ovate to lanceolate, apex pubescent, acuminate, and deciduous.[2-4]

In traditional medical systems all across the world, *H. excelsum's* bark and leaves are primarily used to cure a variety of illnesses. Bark has a variety of medical benefits. Different plant components have reportedly been used to treat emaciation, a carbuncle, a burning sensation in the chest, as well as problems related to lactation and fever. Additionally, it makes you taste and eat more. Inhalation remedy for diarrhoea.[5-6] It has significant *in-vitro* and *in-vivo* antimalarial action since the ethyl acetate extract of *H. excelsum* has showed dose-dependent percentage suppression of *Plasmodium falciparum* schizont formation.[7]

Coumarins[8] and anthraquinones[9], two chemical components previously identified as being present in this plant, were detected. The stem bark of the plant contains tannin, the poisonous alkaloid hymenodictine, aesculin, an apioglucoside of scopoletin, and hymexelsin.[6,10] Additionally isolated from roots are anthraquinones, rubiadin and its methyl ether, lucidin, damnacanthal, nordamnacanthal, 2-benzylzanthopurpurin, anthragallol, soranjidol, and Morindone.[4] Anthragallol, 6-methyalizarin, subiadin, and its 1-methylester, soranjidol, isolated from roots; aesculin (b-methylaesinietin), scopoletin, and hymenodictyonim; alanine, arginine, cystine, glycine, leucine, fruitore, galactose, and glucose,[11]acetylenic fatty acids, a novel triglyceride, and 11 recognised chemicals, including ursolic acid, oleaqnolic acid, uncarinic acid E, and β-sitosterol, have also been reported in studies.[8]

Malaria is the most common infectious disease in Africa and many Asian nations. Malaria is caused by a microscopic protozoon from the Plasmodium species family, which comprises numerous subspecies. A few Plasmodium species can cause illness.[12,13]

Five of the 172 Plasmodium species that exist can infect people. These include *P. knowlesi, P. vivax, P. ovale, P. vivax, P. malariae,* and *P. falciparum.*[13-16] Malaria is a disease that is caused by all of the aforementioned Plasmodium species.[17]

Female Anopheles mosquitos are the only ones that transmit human malaria. After being bitten by an infected female mosquito, the parasite enters the human blood as a sporozoite and travels on to the hepatocytes after 30 minutes of blood circulation.[18]

4RAC Macromolecule: As the only pathway for the synthesis of the purine nucleoside monophosphates necessary for DNA/RNA creation, hypoxanthine, guanine, and [xanthine] phosphoribosyltransferase (HG[X]PRT) is regarded as a crucial target for antimalarial chemotherapy.

In many species, the enzyme hypoxanthine-guanine-[xanthine] phosphoribosyl transferase (HG[X]PRT) plays a vital role. It causes a purine base and a 5′-phospho-D-ribosyl-1-pyrophosphate to combine to generate 6-oxopurine nucleoside monophosphates (PRib-PP).[19]

Therefore, replication should stop if this enzyme is inhibited. The Plasmodium falciparum HGXPRT is effectively inhibited by the aza-acyclic nucleoside phosphonates (aza-ANPs) (Pf HGXPRT).

Although it has been hypothesised for a long time that *Plasmodium falciparum* HGXPRT (PfHGXPRT) could be a target for medications intended to treat malaria[20], inhibitors have only recently been transformed into substances with antimalarial action.[21-22]

However, there are few studies on the phytoconstituents of *Hymenodictyon excelsum* for the antimalarial activity. Thus, keeping the above information in view, the present investigation was designed to identify the potential phytochemicals of *Hymenodictyon excelsum* against 4RAC using a molecular docking method.

2. MATERIALS AND METHODS

2.1. Platform for molecular docking

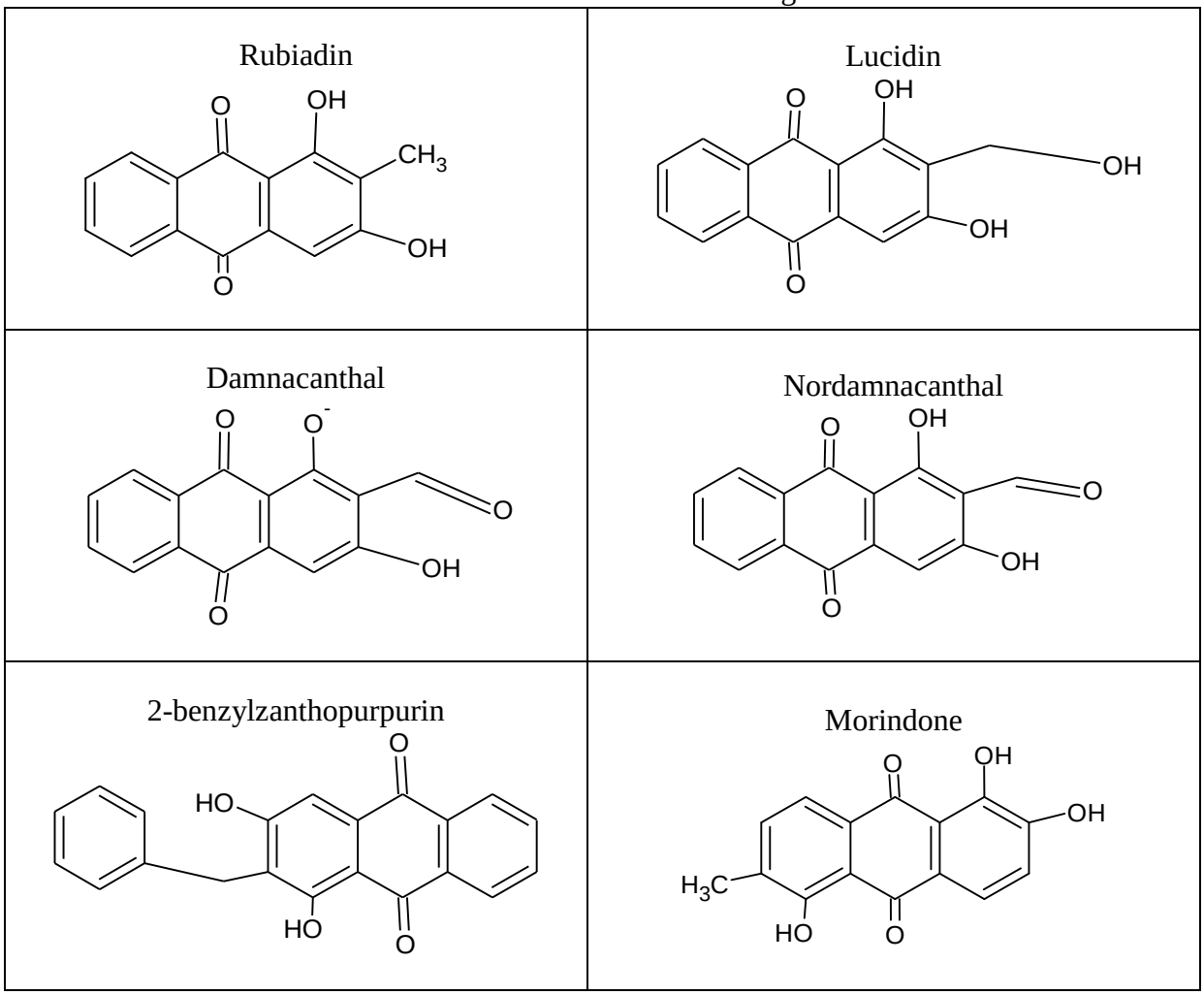
The computational docking study of all the phytoconstituents selected as ligands with antimalarial activity as the target was performed using PyRx software.[23]

2.2. Protein preparation

The macromolecule is 4RAC, *in-silico* analysis of selected phytoconstituents was performed on the 2.05 Å crystal structure of antimalarial macromolecule with inhibitor, (PDB ID:4RAC having resolution: 2.05 Å, R-Value Free: 0.244, R-Value Work: 0.194, R-Value Observed: 0.196), which was retrieved from the protein data bank (https://www.rcsb.org) 4RAC is classified as Tranferase/Transferase inhibitors. all other molecules, such as co-crystallized water molecules, unwanted chains, and nonstandard residues, were deleted. Using Discovery studio.[24]

2.3. Ligand preparation

The three-dimensional (3D) structures of all constituents were retrieved using Avogadro software from the PubChem database available on the NCBI website (https://pubchem.ncbi.nlm.nih.gov/). However, the drawing of geometrical 2D structure was performed using the ChemSketch program. The two-dimensional (2D) structures were transformed into 3D models using the Avogadro software and the ligand structures were saved in the PDB format. All the chemical structures are shown in Figure 1.



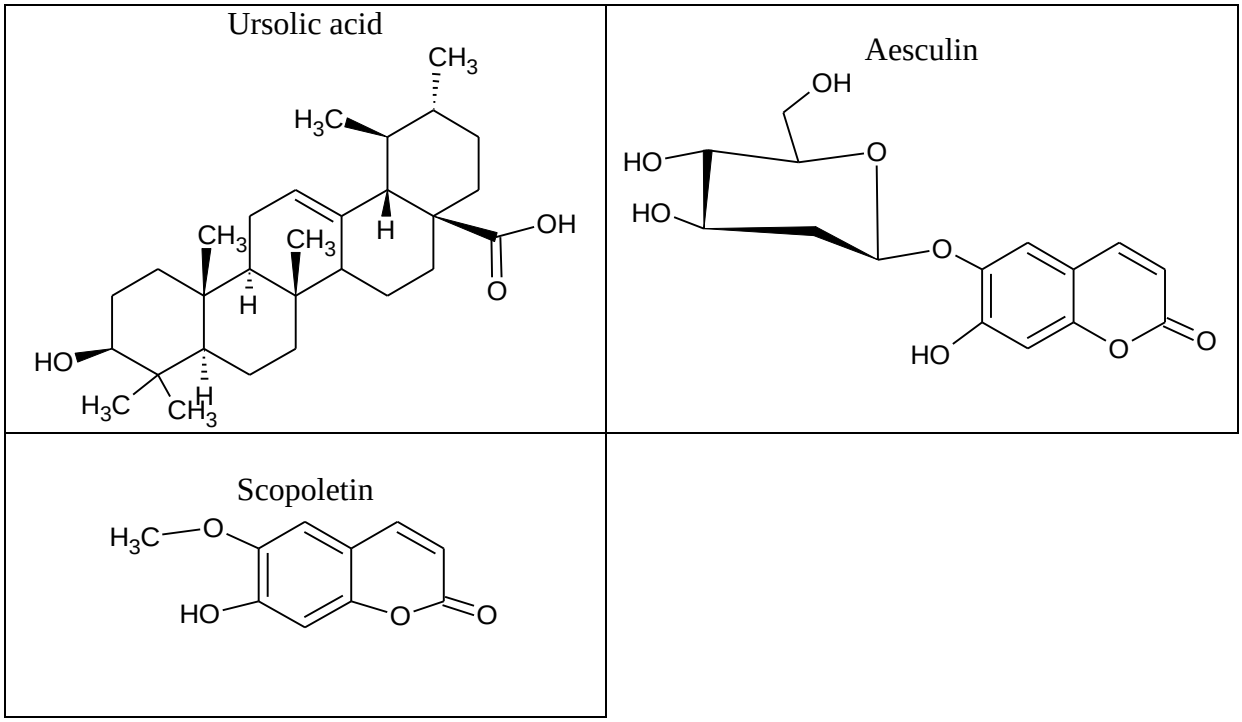


Fig. 1. Chemical structures of all selected phytoconstituents in the molecular docking studies

2.4 Standard Preparation

The standard is prepared steps such as, the 2D structure of standard drug was made using chem sketch program, then the 2D structure was converted into 3D model using Avogadro Software, it was saved in PDB format.

By using PyRx molecular docking of Artemisinin was done with 4RAC.

2.5. Molecular docking

Molecular docking evaluates the protein-ligand interactions and estimates the scoring function based on the geometry to predict the binding affinity of the ligand molecule [25-26]. We applied molecular docking studies to investigate the binding pattern of selected phytoconstituents (Figure 1) and the standard drug, along with the crystal structure of antimalarial activity macromolecule (PDB ID:4RAC). The molecular docking study was performed using PyRxsoftware, Binding affinity was explored using the Vina wizard tool. The final results were analysed and visualized using Discovery Studio 2020 Client [27], with bound ligands as the standard. Visualization of protein ligand interaction reflects the number of interactions and active residues responsible for significant binding at the active site of the target enzyme.

2.6. Absorption, distribution, metabolism, and excretion (ADME) and toxicity prediction

The selected phytoconstituents and standard drug were further checked for drug-likeness properties according to Lipinski's rule. During drug development, it is necessary to predict the tolerability of phytochemicals before being ingested by humans and animal models. The pharmacokinetic profile (ADME) and toxicity predictions of ligands were conducted using SwissADME (http://www.swissadme.ch) and pkCSM (an online server database predicting small-molecule pharmacokinetic properties using graph-based signatures, (http://biosig.unimelb.edu.au/pkcsm/prediction). To analyse the toxicological properties of ligands, Simplified Molecular Input Line Entry System (SMILES) notations or

PDB files were uploaded, followed by selecting the required models for generating numerous information about structure-related effects[28-29].

2.7 Interaction between Proteins by STRING Network Analysis

Search Tool for Retrieval of Interacting Genes (STRING) (https://string-db.org/) Database predicts and integrates protein–protein interaction to identify functional relationships and interactions between proteins. To seek potential interactions between genes involved in DNA Polymerase λ, the STRING tool was employed. STRING provided a platform that postulated several nodes, edges, average node degrees, protein–protein interaction (PPI) enrichment p-values, and average and local clustering coefficient. STRING provided possible biological processes, molecular function, and cellular components of candidate genes studied. [30]

2.8 Bioactivity Score Analysis Using Molinspiration Tool

Molinspiration (http://www.molinspiration.com/cgi-bin/properties) predicts the drug resemblance properties of the compound dependent on various descriptors. Drugs entering the body should tie to an organic molecule to communicate its movement. Along their path, the bioactivity of compounds was anticipated by utilizing the Molinspiration tool which gave a bioactivity score of the phytocompound against the human receptors like GPCRs, ionic channels, kinases, various receptors, proteases, and proteins. A complex is considered to be dynamic if the bioactivity score is more than 0.0, modestly dynamic if somewhere in the range of−5.0 and 0.0, and idle if under−5.0. [31]

3. RESULTS AND DISCUSSION

The present study aimed to explore the inhibitory potential of the phytoconstituents present in *Hymenodictyonexcelsum* targeting antimalarial activity. In this study, we performed molecular docking studies of all phytoconstituents found in *Hymenodictyonexcelsum*using AutoDock Vina, followed by a study of interacting amino acid residues and their influence on the inhibitory potentials of the active constituents. Selected phytoconstituents showing the best fit were further evaluated for absorption, distribution, metabolism, excretion, and toxicological (ADMET) properties using SwissADME and pkCSM servers.

3.1 Molecular docking

The docking scores and binding energies of all chemical constituents of *Hymenodictyonexcelsum*targeting antimalarial activity (PDB ID:4RAC) and binding interactions with amino acid residues are presented in Table 1 respectively.

Table 1. Binding interaction of ligands from *Hymenodictyon excelsum* targeting antimalarial activity (PDB ID:4RAC)

Sr. No.	Chemical constituent	PubChem ID	Docking Score
			4RAC
1.	Rubiadin	124062	-8.2
2.	Lucidin	10163	-8.1
3.	Damnacanthal	2948	-8.4
4.	Nordamnacanthal	160712	-8.9

5.	2-benzylzanthopurpurin	630215	-7.8
6.	Morindone	442756	-8.2
7.	Ursolic Acid	64945	-8.0
8.	Aesculin	5281417	-8.5
9.	Scopoletin	5280460	-6.4
Standard Drug			
10.	Artemisinin	68827	-7.5

The binding affinities of phytoconstituents ranged from – 8.9 to -6.4 kcal/mol. From the docked results, it is evident that the compounds, Nordamnacanthal exhibit the most favourable binding affinity (−8.9 kcal/mol) and in complex with selected macromolecules (PDB ID:4RAC), as compared to other docked compounds i.e. Aesculin (−8.5 kcal/mol), Damnacanthal (−8.4 kcal/mol), Rudiadin(−8.2 kcal/mol), Morindone (−8.2 kcal/mol), Lucidin (−8.1 kcal/mol), 2-benzylzanthopurpurin (−7.8 kcal/mol), Scopoletin (− 6.4 kcal/mol).Visual examination of the computationally docked optimal binding poses of phytoconstituents on selected macromolecules (i.e.4RAC) revealed the significant involvement of various types of interactions, such as hydrogen bonding and hydrophobic interactions, including π–π stacking and π–alkyl and alkyl interactions, in the stability of the binding of the phytoconstituents to 4RAC

The number of intermolecular hydrogen bonds, the binding energy of ligand 4RAC stable complexes, and the number of nearest amino acid residues were also determined for selected compound Artemisinin. All synthesized derivatives formed complexes with target proteins. An analysis of the interaction between the 4RAC protein complex and the Artemisinin ligand was also carried out, which showed that the ligand molecule is oriented due to van der Walls interaction with amino acid residue ILE135, ASP137, THR141, LEU101, GLU133, LEU67, VAL66, GLX70, GLY69, LYS68, ARG199, AP193 were also found (Fig. 2).

An analysis of the interactions between the 4RAC protein complex and the Nordamnacanthal ligand was also carried out, which showed that the ligand molecule is oriented due to one Pi–Pi stacked bond with the PHE186 amino acid fragment, conventional hydrogen bonds interactions with ASP193, ARG199, LYS68, GLY69, Pi-sigma interaction with IEL135, Pi-Alkyl interaction with LEU192, Pi-Anion interaction with ASP134. In addition, six van der Waals interactions with amino acid residues VAL187, LYS165, ASP137, THR141, LEU101, LEU67 were also found (Fig. 3a).

Analysis of interactions of the 4RAC protein complex and ligand Rubiadin showed that the ligand molecule is oriented due to one Pi–Pi Stacked bond with the PHE186 amino acid fragment and to Pi-sigma interactions with amino acid residues ILE135, and forming conventional hydrogen bonds with ARG199, ASP193, residues and Pi-Alkyl interaction with LEU192, and Unfavorable Donar interaction with PHE186, and Pi-Anion interaction with ASP134. In addition, seven van der Waals interactions with amino acid residues VAL187, LYS165, ASP137, THR141, LEU101, LUE67, GLX69 were also found (Fig. 3b).

An analysis of the interactions between the 4RAC protein complex and the Lucidin ligand was also carried out, which showed that the ligand molecule is oriented due to one Pi–Pi stacked bond with the PHE186 amino acid fragment, conventional hydrogen bonds interactions with the amino acid residues ASP193, LEU67, GLY69 Pi-sigma interaction with IEL135 Pi Alkyl interaction with LEU192, Unfavorable donar interaction with ARG199, Pi-Anion interaction with ASP134. In addition, eight van der Waals interactions with amino acid residues VAL187, LYS165, ASP137, THR141, LEU101, ARG100, VAL66, LYS68 were also found (Fig. 3c).

Table 2. Binding interactions of ligands with the binding site of Hypoxanthine-guanine phosphoribosyltransferase (HPRT1)

Sr. No	Inhibitors	Binding energy (kcal/mol)	H bond	Main amino acid interaction	
				Pi-alkyl, Pi-Sigma, alkyl, Pi-S/Pi-Pi stacking/Pi-Pi T shaped/halogen/unfavourable donor-donor interactions	van der Waals interaction
1	Rubiadin	-8.2	ARG199, ASP193	PHE186, ILE135, LEU192, PHE186, ASP134	VAL187, LYS165, ASP137, THR141, LEU101, LEU67, GLY69
2	Lucidin	-8.1	ASP193, LEU67, GLY69	PHE186, ILE135, LEU192, ARG199, ASP134	VAL187, LYS165, ASP137, THR141, LEU101, ARG100, VAL66, LYS68
3	Damnacanthal	-8.4	ASP193, ARG199,LYS68	PHE186, ILE135, LEU192, ASP134	VAL187, LYS165, ASP137, THR141, LYS102, LEU101, ARG100, LEU67, GLY69
4	Nordamnacanthal	-8.9	ASP193, ARG199, LYS68, GLY69	IEL135, PHE186, LEU192, ASP134	VAL187, LYS165, ASP137, THR141, LEU101, LEU67
5	2-benzylzanthopurpurin	-7.8	ASP193	LEU192, ILE113, ILE135, ASP134, THR141	LEU101, LYS102, ASP137, LYS165, VAL187, ARG199, GLY69, LYS68
6	Morindone	-8.2	LEU67, ASP193, ARG199, LYS68, LEU192	PHE186, ASP134	VAL187, LYS165, ASP137, GLY69, ARG100, LEU101
7	Aesculin	-8.5	VAL187, LYS165, ASP193	PHE186, ILE135, LEU192, ASP134	LYS185, LYS102, LEU101, GLU133, LYS68, GLY70, VAL66, GLY69, LEU67, ARG199
Standard Drug					
8	Artemisinin	-7.5	No Interaction	No Interaction	ILE135, ASP137, THR141, LEU101, GLU133, LEU67, VAL66, GLY70, GLY69, LYS68, ARG199, AAP193

3.2. ADMET study

Pharmacokinetic profile (ADME) and toxicity predictions of the ligands are important attentive parameters during the transformation of a molecule into a potent drug. In the present study, these parameters were assessed using SwissADME and pkCSM. The absorption potential and lipophilicity are characterized by the partition coefficient (Log *P*) and topological polar surface area (TPSA), respectively. For better penetration of a drug molecule into a cell membrane, the TPSA should be less than 140 Å. However, the value of Log *P* differs based on the drug target. The ideal Log *P* value for various drugs are as follows: oral and intestinal absorption, 1.35 −

1.80; sublingual absorption, > 5; and central nervous system (CNS)[32]. The aqueous solubility of ligands ideally ranges from − 6.5 to 0.5 [33], while the blood brain barrier (BBB) value ranges between − 3.0 and 1.2 [34]. In addition, non-substrate P-glycoprotein causes drug resistance [35]. In our study, all the selected ligands followed the TPSA parameter, P-glycoprotein non-inhibition, thereby showing good intestinal absorption and an acceptable range of BBB values. All the compounds showed aqueous solubility values within the range. Further, it was predicted that the selected ligands do not show AMES toxicity, hepatotoxicity, and skin sensitivity. In addition, it did not inhibit hERG-I (low risk of cardiac toxicity). Lipinski's rule violations, *T. pyriformis* toxicity, minnow toxicity, maximum tolerated dose, rat acute oral toxicity, and chronic toxicity are depicted in table 3.

Table 3. ADME and toxicity predicted profile of ligands with superior docking scores

ADMET Properties	**Formula**	**MW (g/mol)**	**Log P**	**TPSA (Å^2)**	**HB doner**	**Hb acceptor**	**Aqueous solubility (Log mol/L)**	**Human intestinal absorption (%)**	**Blood-brain barrier**
Rubiadin	$C_{15}H_{10}O_4$	254.24	2.18162	74.60	2	4	-3.243	96.938	0.025
Lucidin	$C_{15}H_{10}O_5$	270.24	1.3655	94.83	3	5	-2.963	70.752	-0.979
Damnacanthal	$C_{15}H_7O_5$	267.21	1.0537	94.50	1	5	-3.04	83.174	-0.288
Nordamnacanthal	$C_{15}H_8O_5$	268.22	1.6857	91.67	2	5	-3.08	92.837	-0.157
2-benzylzanthopurpurin	$C_{21}H_{14}O_4$	330.33	3.464	74.60	2	4	-4.133	96.885	0.187
Morindone	$C_{15}H_{10}O_5$	270.24	1.88722	94.83	3	5	-3.093	74.498	-0.707
Ursolic Acid	$C_{29}H_{46}O_3$	442.684	6.6994	57.53	2	2	-4.508	96.081	-0.384
Aesculin	$C_{15}H_{16}O_8$	324.28	-0.2935	129.59	4	8	-2.482	69.689	-1.298
Scopoletin	$C_{10}H_8O_4$	192.17	1.5072	59.67	1	4	-2.467	95.015	-0.309
Standard Drug									
Artemisinin	$C_{15}H_{22}O_5$	282.33	2.3949	53.99	0	5	-3.678	97.543	0.235

Table 3 Continued

ADMET Properties	PGP substrate	Total clearance [Log mL./(min.kg)]	Bioavailability score	AMES toxicity	Max tolerated dose [Log mg/(kg.d)]	hERG I inhibitor	hERG II inhibitor
Rubiadin	YES	0.129	0.55	YES	0.387	NO	NO
Lucidin	YES	0.073	0.55	NO	0.761	NO	NO
Damnacanthal	YES	0.223	0.56	YES	0.077	NO	NO
Nordamnacanthal	YES	-0.024	0.55	NO	0.645	NO	NO
2-benzylzanthopurpurin	YES	0.167	0.55	YES	0.199	NO	YES
Morindone	YES	-0.046	0.55	YES	0.556	NO	NO
Ursolic Acid	YES	0.13	0.85	NO	-0.809	NO	NO
Aesculin	YES	0.765	0.55	NO	0.0543	NO	NO
Scopoletin	NO	0.752	0.55	NO	0.292	NO	NO
Standard Drug							
Artemisinin	NO	0.98	0.55	YES	0.065	NO	NO

Table 3 Continued

ADMET Properties	Acute oral rat toxicity, LD50(mol/kg)	Oral rat chronic toxicity (Log mg/kg bw/day)	Hepatotoxicity	Skin sensitisation	T. Pyriformis toxicity (Log µg/L)	Minnow toxicity (Log mmol/L)	Lipinski's rule violations
Rubiadin	2.146	1.554	NO	NO	0.848	0.364	YES (0)
Lucidin	2.283	2.359	NO	NO	0.382	0.457	YES (0)
Damnacanthal	1.998	1.602	NO	NO	0.975	0.678	YES (0)
Nordamnacanthal	1.57	2.389	NO	NO	0.629	2.071	YES (0)
2-benzylzanthopurpurin	2.21	1.345	NO	NO	0.298	-0.995	YES (0)
Morindone	2.124	2.215	NO	NO	0.421	1.904	YES (0)
Ursolic Acid	4.018	2.02	YES	NO	0.315	-0.229	YES (1)
Aesculin	2.417	3.255	YES	NO	0.282	2.865	YES (0)
Scopoletin	2.012	1.424	NO	NO	0.453	1.604	YES (0)
Standard Drug							
Artemisinin	2.459	1	NO	NO	0.322	1.406	YES (0)

3.3 String Pathway

Hypoxanthine-guanine phosphoribosyltransferase (HPRT1): Converts guanine to guanosine monophosphate, and hypoxanthine to inosine monophosphate. Transfers the 5-phosphoribosyl group from 5-phosphoribosylpyrophosphate onto the purine. Plays a central role in the generation of purine nucleotides through the purine salvage pathway.

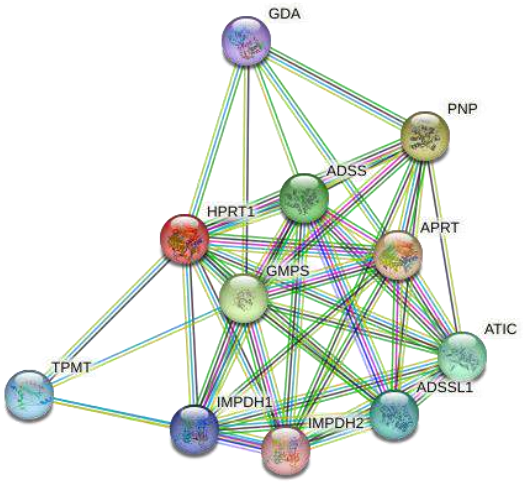


Fig.2. Network formation of HPRT1 using STRING

3.4 Molinspiration

Lastly, we predicted bioactivity scores to identify the potency of Phyto molecules studied (Table 4). Our result showed that nordamnacanthal, rubiadin and lucidin might essentially serve as an interface with Hypoxanthine-guanine phosphoribosyltransferase (HPRT1) as they acted as enzyme inhibitors. Bioactivity scores of phytoconstituents and standard were comparable indicating that these phytocompounds might be utilized as an alternative and in improving treatment to malaria.

Table 4. Summary of predicted Molinspiration bioactivity score for nordamnacanthal, rubiadin and lucidin in comparison to Artemisinin

Bioactivity	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Nordamnacanthal	-0.20	-0.04	0.10	0.15	-0.28	0.22
Rubiadin	-0.20	-0.19	-0.03	0.07	-0.26	0.24
Lucidin	-0.02	0.04	0.13	0.19	-0.02	0.38
Standard Drug						
Artemisinin	-0.17	-0.31	-0.65	-0.00	-0.19	0.39

Standard Drug

1. Artemisinin,4RAC

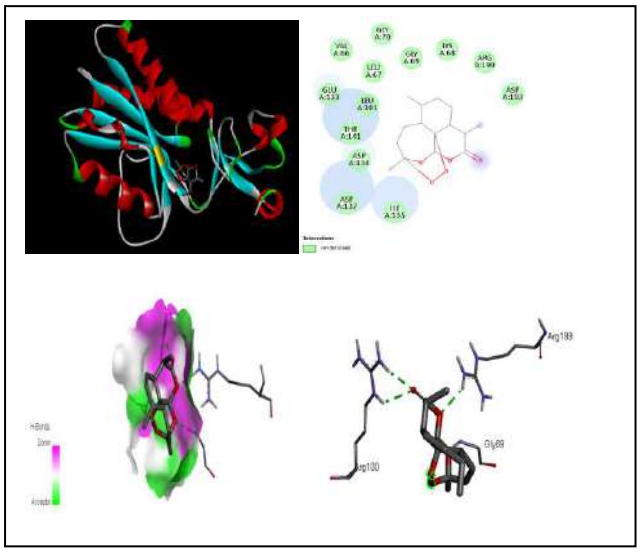
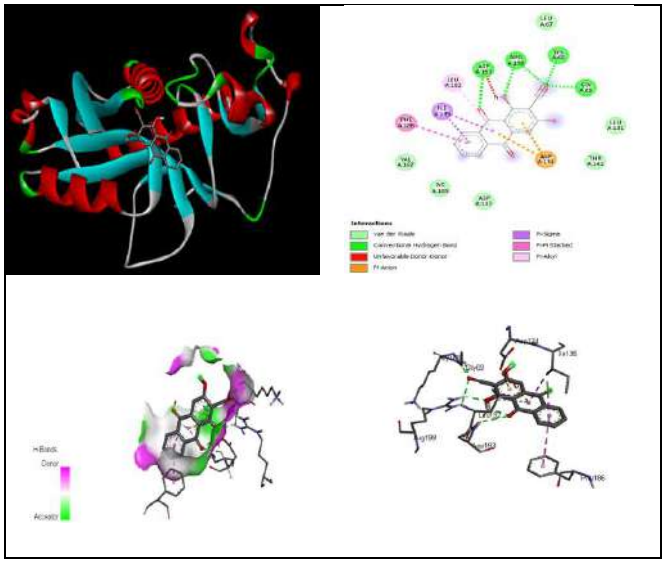


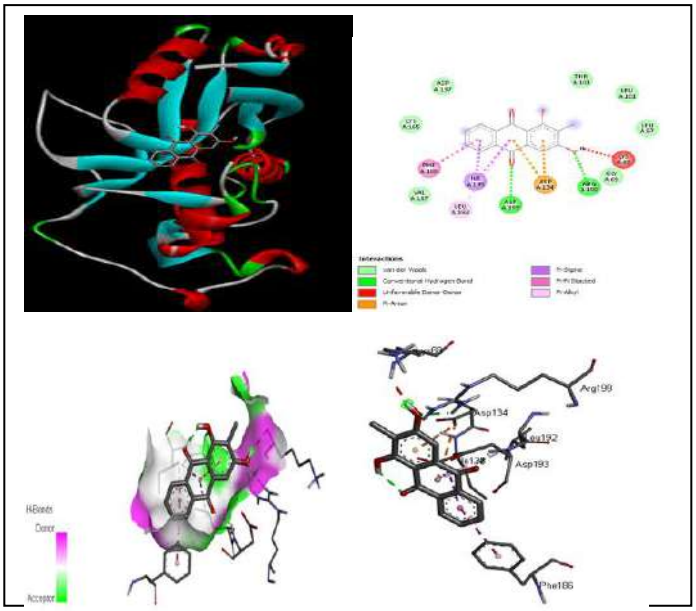
Fig. 3. Docking scores and binding interaction of Artemisinin (PDB ID: 4RAC).
The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

Drugs to be considered

a. Nordamnacanthal



b. Rubiadin



c. Lucidin

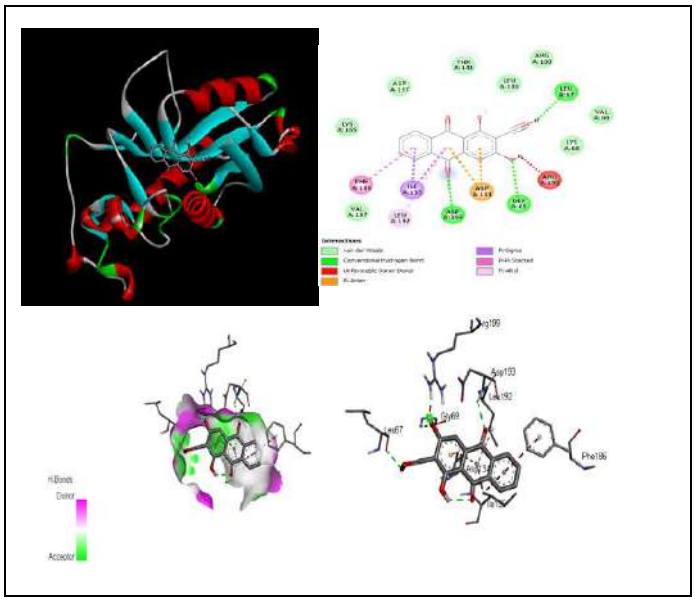


Fig. 4. Docking scores and binding interaction for antimalarial activity (PDB ID: 4RAC). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction

Boiled Egg Diagram

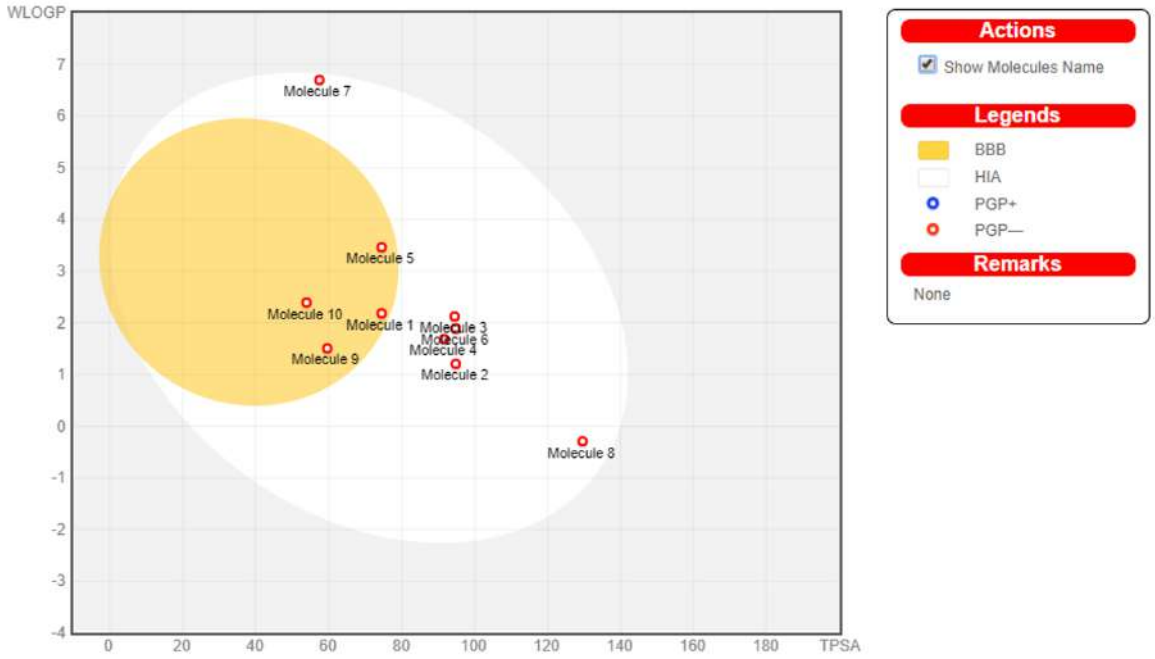


Fig. 5 Combined boiled egg diagram of all phytoconstituents with standard.

Table 5. Molecule names in boiled egg diagram.

MOLECULES NO.	DRUG NAME
1	Rubiadin
2	Lucidin
3	Damnacanthal
4	Nordamnacanthal
5	2-benzylzanthopurpurin
6	Morindone
7	Ursolic acid
8	Aesculin
9	Scopoletin
10	Artemisinin

BOILED means **B**rain **O**r **I**ntestina**L** **E**stimate **D** Permeation Predictive model:
The Boiled egg diagram shows two regions white and yellow. The white region is the physiochemical space of molecules with highest probability of being absorbed by the gastrointestinal tract, and the yellow region (yolk) is the physiochemical space of molecules with highest probability to permeate to the brain.
In addition the points are coloured in blue if predicted as activated effluxed by P-gp (PGP+) An in red if predicted as non-substrate of P-gp (PGP).

CONCLUSION

In this study, we have carried out an *in-silico* screening of the phytoconstituents of *Hymenodictyon excelsum* plant. This study demonstrated the nine compounds from *Hymenodictyon excelsum* plant, (Rubiadin, Lucidin, Damnacanthal, Nordamnacanthal, 2-bezylzanthopurpurin, Morindone, Ursolic Acid, Aesculin, Scopoletin). The selected phytocompounds showed docking scores ranging from – 8.9 to -6.4 kcal/mol in 4RAC. Among all, Nordamnacanthal gave the lowest binding energy (− 8.9 kcal/mol) in complex with 4RAC

whereas the reference compound, Artemisinin, showed a docking score with a binding energy –7.5kcal/mol. Furthermore, these ligands exhibited good ADMET properties. To summarize, phytoconstituents present in *Hymenodictyon excelsum* possess strong effects against 4RAC and could be further evaluated for their anti-malarial effect, as well as for the development of alternative drugs with fewer side effects for the treatment of malaria.

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70

Spectrophotometric Complexation Study of Cu(II) with 8-Hydroxyquinoline based Azo dye

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Abstract:

In present study Cu(II) and 8-Hydroxyquinoline azo dye (8-HDQ-Cu(II)) were combined to generate a metal complex, which was then examined using IR, UV-Visible and Scanning electron microscopic methods. The complex formation spectroscopic peak is visible at 305 nm. The binding constant and the 1:2 M:L stoichiometry have been ascertained. As a result, the azo dye of 8-hydroxyquinoline is a commonly used indicator in the complexometric method to measure Cu(II).

Keywords: 8-Hydroxyquinoline, Cu(II) metal ion, UV-Visible

Introduction:

Potential applications in industry, technology, and life processes have been identified for coordination complexes containing azo chemicals as ligands[1-4]. Copper complexes have many different and significant applications. Copper complexes find extensive application as fungicides, crop defenders, and polymer additives. Metal complex dyes are essential functional materials that have been incorporated into numerous high-tech applications. The creation of innovative azo dye structures has drawn attention; many of these structures are beneficial for commercial applications such as polyester, polyamide, and polyacrylic, as well as blends with other fibers [5-7]. 8-Hydroxyquinoline (8-HQ), a crucial ligand in this area, is well-known for its potent coordination skills and special capacity to distinguish between various metals [8]. In order to use 8-hydroxyquinoline and its derivatives, the phenolate oxygen and quinoline nitrogen must connect both inside and outside of the cyclic structure. This makes it possible to use it as a metal chelator because it can bind to metals in bidentate and monomeric forms [9].

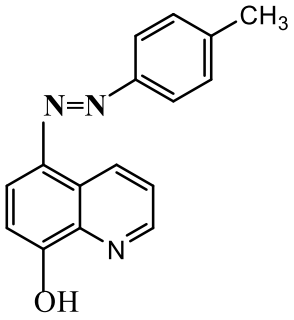


Figure 1: 8-Hydroxyquinoline azo dye

Chemicals and Instruments:

S.D. Fine Chemicals provided all of the chemical substances used in this investigation. A single beam UV-VIS Bio-Era spectrophotometer with a quartz cell (10 mm) was used to measure the electronic spectra, and an IR spectrometer made by Brucker was utilized to get the FT-IR spectra. Additional double-distilled water purification was supplied by Milli-Q. The AR grade of solvents was used. The 8-HDQ dye stock solution contained 2×10^{-4} M, while the metal solutions had 1×10^{-2} M.

Preparation of Ligand and Complex:

The preparation of ligand and its complex was prepared according previously reported literature [10].

UV-Visible Study of ligand and its Cu(II) complex:

The UV-visible spectroscopic approach was used to characterize the study using a UV-visible spectrophotometer with a 10 mm quartz cell. This is the spectrum of an ethanol solution of copper nitrate (5×10^{-4}M) and ligand (5×10^{-5}M) in water after adding some concentrated nitric acid. It was noted from the graph (Fig.2) that the ligand exhibits its greatest absorbance at 305 nm, which is the cause of n-π*. However, there is a little shift up to 295 nm that shows the complex formation during complexation with copper metal ion.

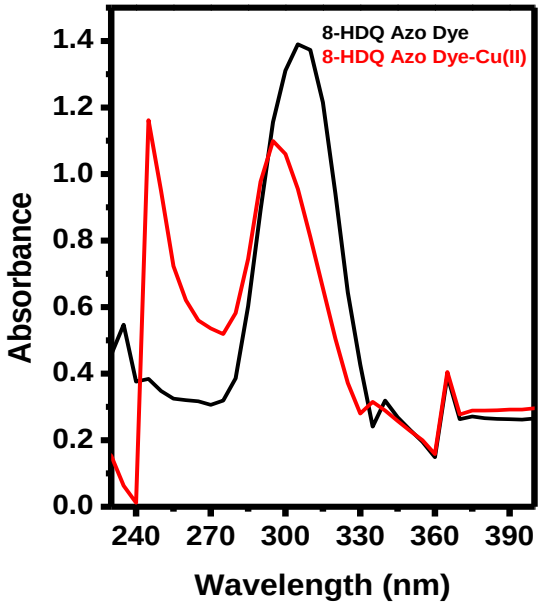


Figure 2: UV-Visible spectra of ligand and its Cu(II) Complex

Metal to ligand stoichiometry:

Cu(II) metal ion solutions and 8-HDQ azo dye were combined in similar mole ratios, with the dye and metal ion concentrations being constant. The complex's stoichiometry was ascertained by measuring the absorbance at a wavelength of 305 nm. The relationship between absorbance and mole fractions is depicted in Figure 3, the resultant absorbance graph. For the 8-HDQ-Cu(II) complexes, the greatest absorbance is observed at a mole ratio of 0.4, indicating that two ligands are bonded to the metal ion in a 1:2 ratio.

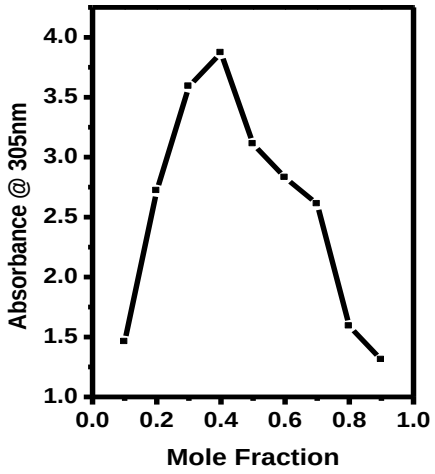


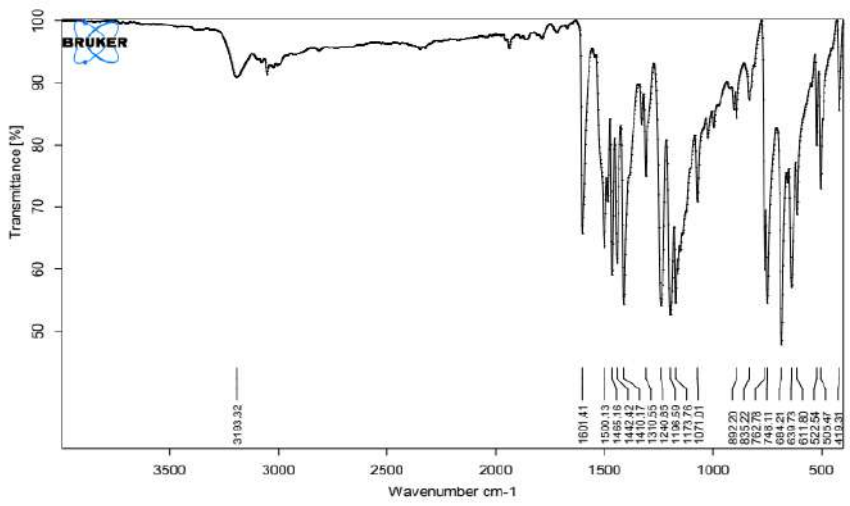
Figure 3: Jobs plot of Complex fot the stoichiometry

IR Spectra Study:

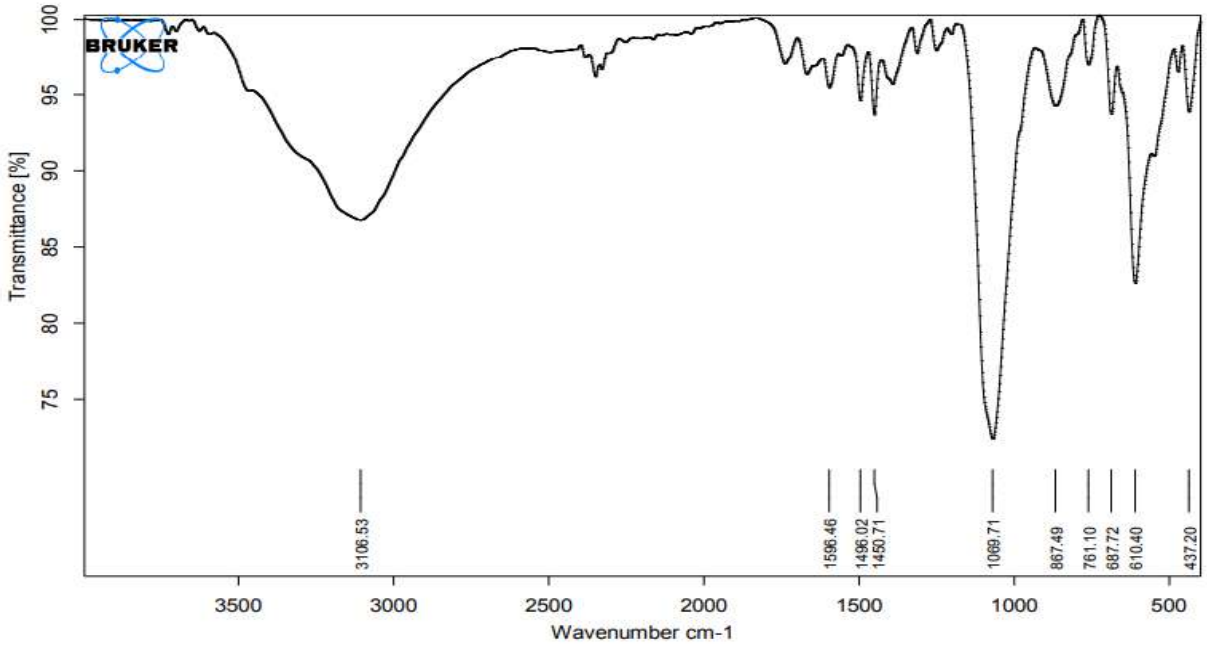
The FTIR spectra of the developed complexes and ligands are shown in Figure 4. Table 1 displays the spectrum data obtained from FTIR spectroscopy. A broad band of moderate intensity was seen on the ligands. The O-H bond of 8-HDQ ligands appeared at 3193 cm^{-1} in the FTIR spectra, however, it moved to 3106 cm^{-1} when the complex formed with the Cu(II) metal ion. In 8-HDQ, a band confirming the presence of the C-O bond was found at 1240 cm^{-1} however, in the complexes, these bands migrated to 1230 cm^{-1}. The vibrational frequencies of the M-O and M-N bonds support the confirmation of the bonding between the ligand and metal ion. These frequencies are roughly 602 cm^{-1} for the former and 437 cm^{-1} for the latter.

Table 1. Infra-red spectral data for 8-HDQ and Co(II) complexes.

	Infra red spectral bands υ cm^{-1}					
Compound	OH	C-O	C-N	N=N	M-O	M-N
8-HDQ	3193	1240	1310	1465	-	-
8-HDQ-Cu(II)	3106	1230	1305	1450	610	437



(a)



(b)

Figure 4: IR spectra of (a) 8-HDQ (b) 8-HDQ-Cu(II) complex

The stability constant of 8-HDQ-Cu(II) complex:

The stability constant, sometimes referred to as a binding constant, is the equilibrium constant for complex formation in solution. It serves as an indicator of how well the metal and ligand will bind together to form a complex. The following equation was used to determine the apparent stability constant (K) of the (1:2) Metal: Ligand complex with the use of spectroscopic data.

$$K=1-\alpha/4\alpha^3c^2 \quad (1)$$

$$\alpha = A_m-A_s/A_m \quad (2)$$

or $\alpha = A_S-A_m/A_s$

where, A_S is the solution's absorption when ligand and metal ions are present in stoichiometric proportions, c is the complex solution's concentration in mol/L, and A is the degree of dissociation. Am=is the quantity of metal absorbed in a solution containing an excess of ligand. The solution's λmax was used to assess the values of A_S and A_m. The values of α, K, A_m, and A_S were tabulated below Table 2, which demonstrates the high value of K, or 2.3×10^5. This outcome demonstrates the strong binding between Cu(II) metal and 8-HDQ azo dye.

Table 2. The stability constant of 8-HDQ-Cu(II) Complex:

complex	A_S	A_m	α	K_S
$[Bi(L)_2]$	2.233	2.595	0.01325	2.3×10^5

Scanning Electron Microscopy Study:

The morphologies of 8-HDQ, and its Cu(II) complexes were investigated in the scanning electron microscopy (SEM) study. The SEM pictures of the ligands exhibit an irregular, rock like morphology with varying lateral diameters, as illustrated in Fig. 5(a,b). It's interesting to note that the complexes' surface shape was significantly changed by metal coordination to the ligand. In particular, the copper complex's SEM micrographs show a noticeably uneven structure that resembles broken ice.

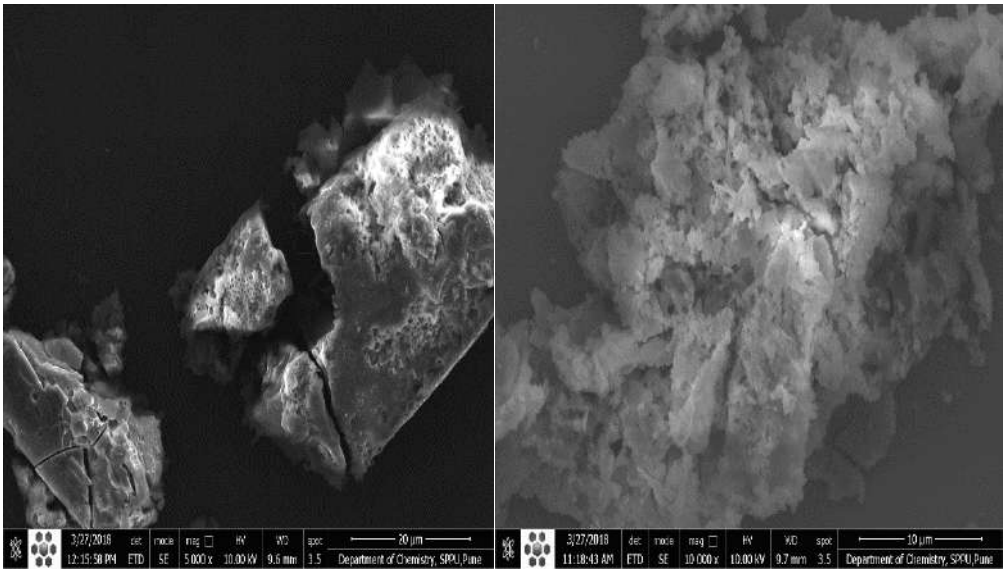


Figure 5: SEM micrograph of (a) 8-Hydroxyquinoline azo dye and (b) 8-HDQ-Cu(II) complex

Conclusion:

In summary, we have effectively created an 8-hydroxyquinoline compound using Cu(II). UV-Vis spectroscopy has been used to study Cu(II)binding with 8-HDQ. After research, the stoichiometry of metal ions and ligands was found to be 1:2. The complex that forms between copper and the azo dye of 8-hydroxy quinoline has a larger stability constant, indicating that it is stable. Additional evidence of the binding relationship between Cu(II) and ligand is provided by SEM studies and IR spectra.

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71

A Comprehensive Review on Various Method of Synthesis and Biological Activities of Schiff Bases with Heterocyclic Moiety

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Abstract:

Schiff bases are versatile chemical compounds that are becoming more important because of their numerous applications. Schiff bases, which include imines or azomethine functional groups, are formed by the condensation of primary amines with carbonyl compounds or can exist naturally in plants. They are widely used in industry and exhibit a variety of biological activities, such as antibacterial, antifungal, antiviral, and anticancer properties. Researchers are presently focusing on a wide range of biological studies of Schiff bases, which could lead to the discovery of new lead compounds. This review covers discoveries and various methods for synthesising specially Schiff bases with heterocyclic moiety, as well as their biological functions.

Keywords: Schiff bases; Biological activities; Applications; Antifungal; Antiviral; Anticancer

Introduction



Figure 1. A portrait of Hugo Schiff

Hugo Schiff (1834–1915) (Figure 1) was a German scientist. He discovered some bases and named them Schiff bases [1]. Schiff bases are generated by reacting a primary amine with carbonyl compounds (aldehydes or ketones) under specific conditions. The common structure is R1R2C=NR (R ≠ H), with the main function being the imine or azomethine (-C=N-) group (Figure 2) [2].

Schiff bases, particularly those coupled to a heterocyclic moiety, displayed a wide range of pharmacological and biological actions, including antibacterial, cytotoxic, antifungal, antimalarial, anticonvulsant, antioxidant, and anti-inflammatory properties [3–10]. Schiff base used in different field given below in Fig.3.

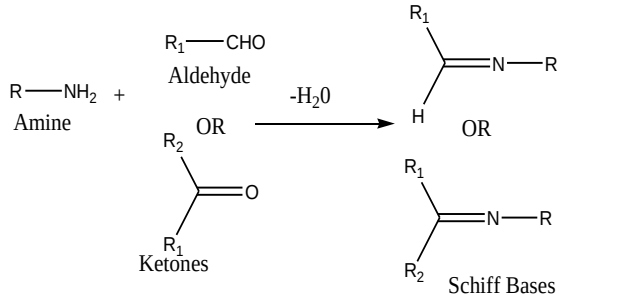


Figure 2

R_1,R_2 and/or R_2= Alkyl or Aryl group

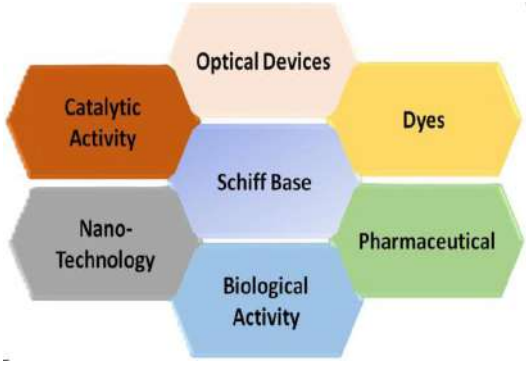
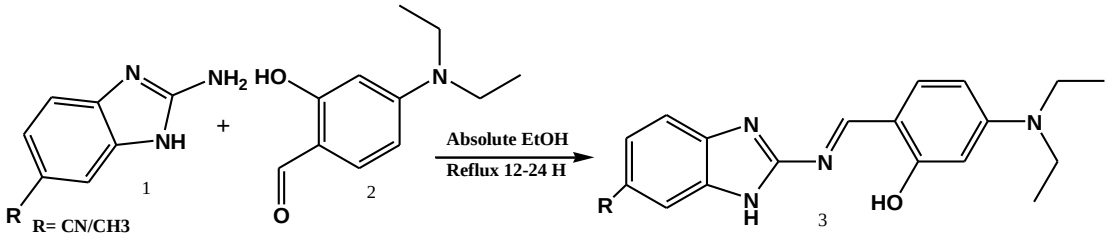


Fig. 3

Various Synthesis Methods for Schiff Bases: Schiff bases have been employed in a variety of industries. As a result, many approaches and innovative procedures for the preparation of Schiff bases have been documented, including the following:

i) Conventional or common heating method:

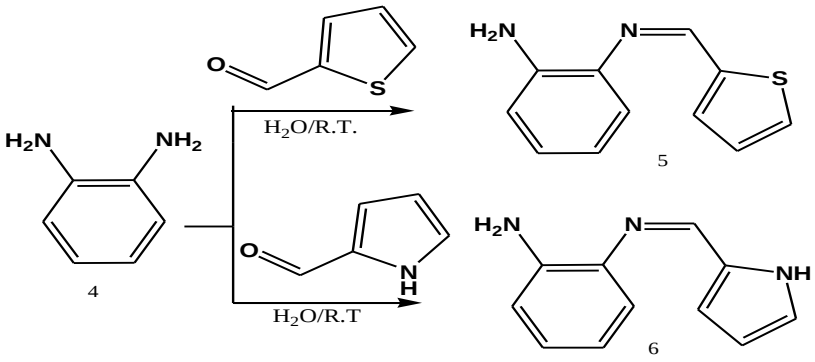
The Schiff base containing benzothiazole moiety 3 was made by reacting 2-amino-6-methylbenzothiazole 1 with 5-bromo-2-hydroxybenzaldehyde 2 in ethanol as a solvent and refluxing the reaction mixture for two hours. [11] (Scheme 1).



Scheme 1

ii) Using water as a solvent:

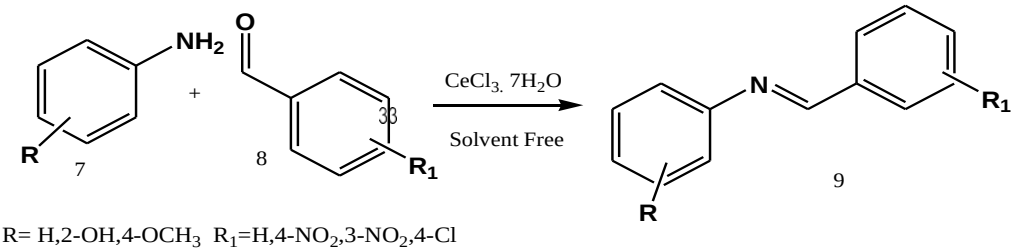
Mono-Schiff bases **5** and **6** were prepared by the stirring of 1,2-diaminobenzene **4** with thiophene-2-carbaldehyde and 1*H*-pyrrole-2-carbaldehyde, respectively, in H_2O as a solvent.[12]



SScheme 2

iii) Metal catalyzed:

Cerium (III) chloride catalyzed: Schiff base **9** was produced by the reaction of aromatic amines 7 with aldehydes 8 in the presence of $CeCl_3.7H_2O$ as a catalyst under solvent-free conditions. [13] (Scheme 3).

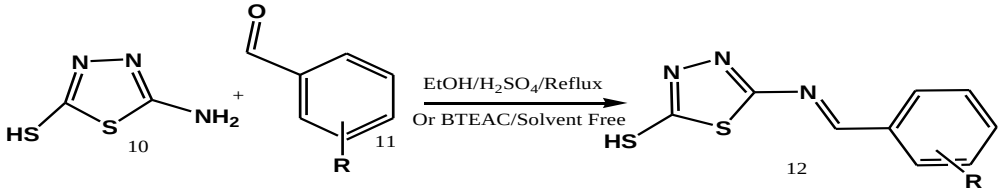


R= H,2-OH,4-OCH_3 R_1=H,4-NO_2,3-NO_2,4-Cl

Scheme 3

iv) Acidic and phase transfer catalyst (PTC) conditions:

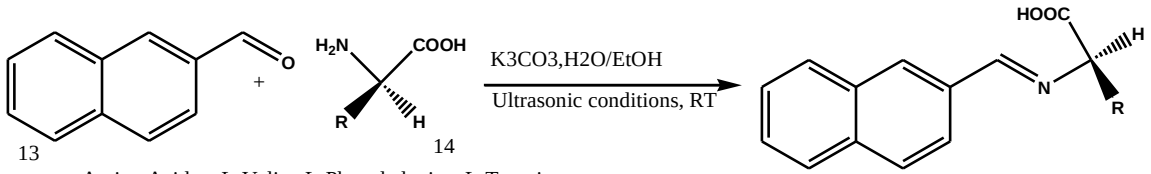
The reaction of 2-amino-5-mercapto-1,3,4-thiadiazole **10** with aromatic aldehydes **11** in ethanol in the presence of H_2SO_4 (acidic conditions) produced 1,3,4-thiadiazole Schiff bases **12.** Benzyl triethylammonium chloride (BTEAC) was also used as a catalyst during the process solvent-free [14] (Scheme 04**)**



R= 2-OCH_3,2-Cl,3-Br,4-NMe,4-F,4-OCH_2Ph

v) Ultrasonic and microwave conditions

Chiral-Schiff bases **15** were synthesized by ultrasonically reacting 2-naphthaldehyde **13** with chiral α- amino acids **14** in the presence of K_2CO_3.[15]



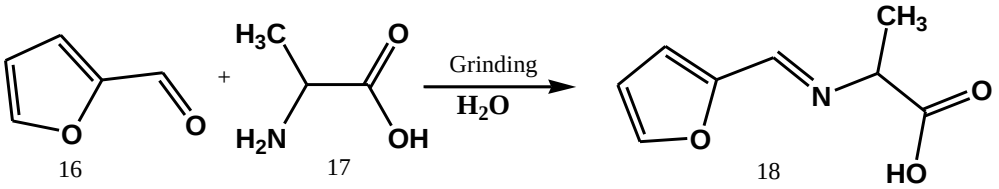
13 14 15

Amino Acids = L-Valine,L-Phenyl alanine, L-Tyrosine
L-Aspartic Acid, L-Methionine

Scheme 5

vi) Grinding chemistry technique:

The synthesis of bioactive chemicals was carried out using grindstone technology. Furan-2-carbaldehyde **16** and DL-alanine **17** were reacted in water as a green solvent to produce Schiff base (E)-2-(furan-2-ylmethyleneamino) propanoic acid **18** [16].



16 17 18

Scheme 6

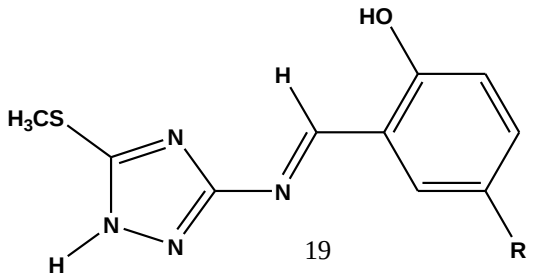
Biological activities of Schiff bases :

Antimicrobial activities:

Triazole-Schiff bases **19** showed strong antibacterial activity against Escherichia coli, Salmonella typhi, and Bacillus subtilis. In addition, they had significant antifungal activity against Candida albicans, Aspergillus flavus, Fusarium solani, and Candida glabrata. [17] (**Figure 4**).

Isatin-Schiff base **20** showed significant antibacterial action against pseudomonas aeruginosa (MIC = 6.25 mg/mL) [18] (Figure 5).

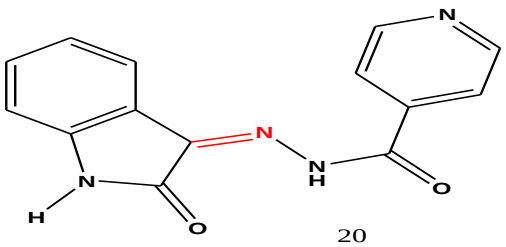
Acetylenic indole-Schiff base **21** shown antibacterial activity against Staphylococcus aureus, with a MIC of 7.81 µM. Indole-Schiff base **22** showed antifungal efficacy against Candida krusei, with a MIC of 15.62 µM [19] (Figure 6).



19

R=H,Cl,Br,NO2

Fig. 4 Triazole-Schiff bases



20

Fig. 5

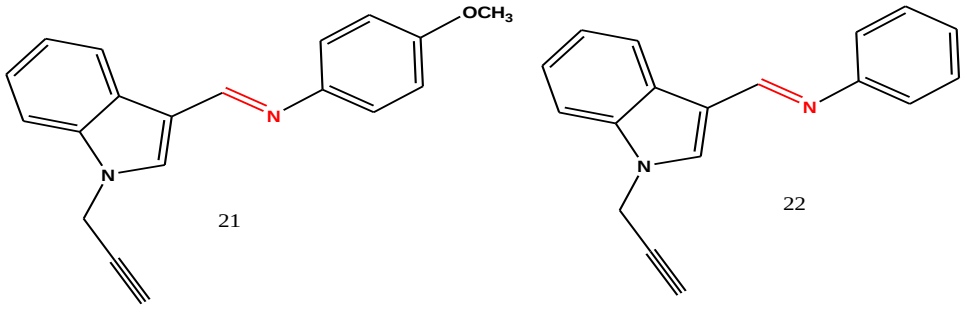


Figure 6. Acetylenic indole-Schiff bases

Piperazine-sulphonamide-linked to Schiff base **23** showed potent antibacterial activity against *Bacillus subtilis* with MIC= 26.1 µg/mL [20] (**Figure 7)**.

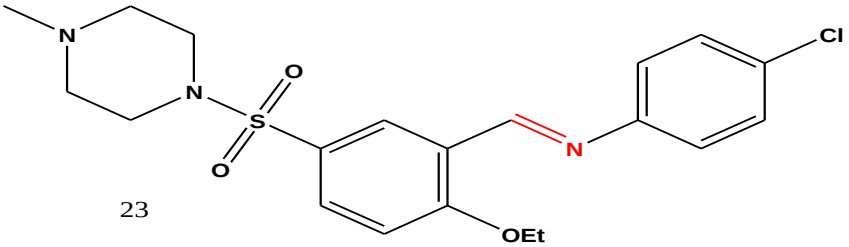


Figure 7 Piperazine-sulphonamide linked to Schiff base 6

Anticancer activities:

1,3,5-Triazine-isatin Schiff base **24** showed anticancer activities against lung (HOP-92), leukemia(CCRF-CEM), and leukemia (SR) cancer cell lines [21] (**Figure 8).**

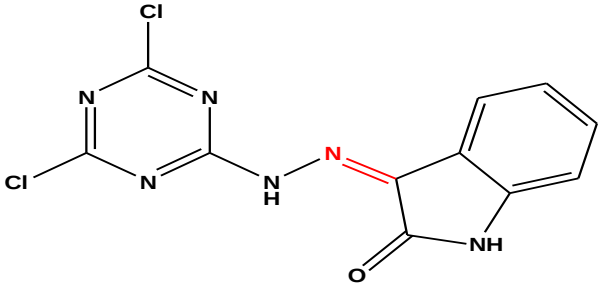


Fig.8 1,3,5-Triazine-isatin Schiff base 24

Anti-inflammatory activities:

Schiff base based on quinazolin-4-one in combination with 1, 3, 4-oxadiazole moiety **25** showed anti-inflammatory effects [22] (Figure 9).

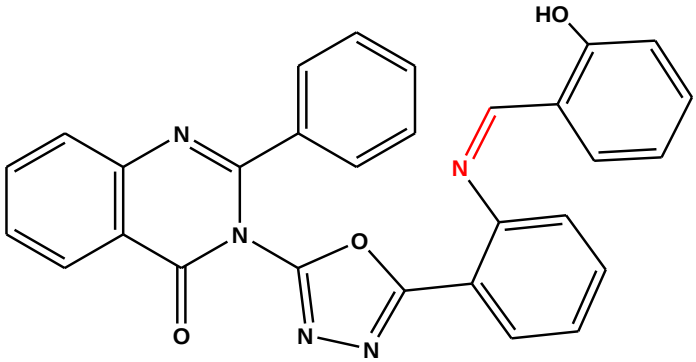


Fig. 9 Schiff base based on quinazolin-4-one with 1,3,4-oxadiazole 25

Analgesic activities: Isatin-Schiff base 26 exhibited good analgesicactivity [23] (Figure 10).

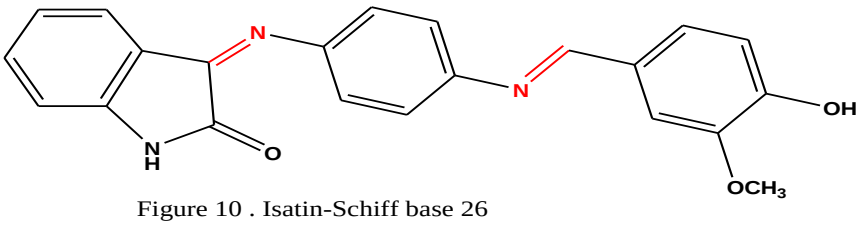


Figure 10 . Isatin-Schiff base 26

Anthelmintic activities:

Antipyrine-coumarin linked to Schiff bases **27** showed excellent anthelmintic activities [24]**(Figure 11)**.

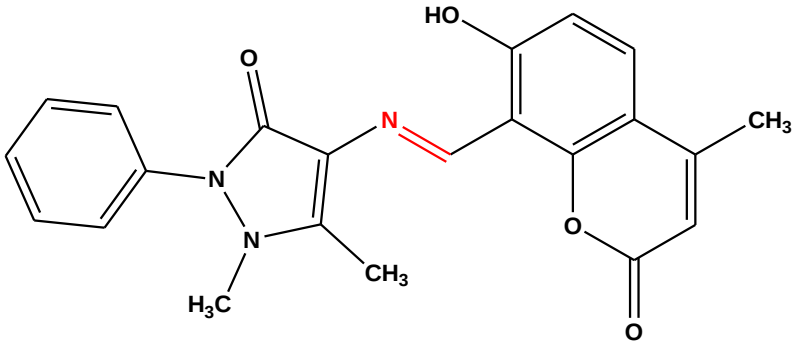
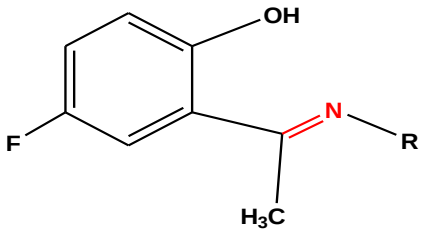


Figure 11 Antipyrine-coumarin linked to Schiff bases 27

Antioxidant activities:

Halogenated Schiff bases **25** showed very low to moderate antioxidantactivities [24] (**Figure 12**).



R= C_3H_7,C_5H_{11},C_6H_{13},C_7H_{15}

Figure 12. Halogenated Schiff bases 28

Conclusion:

Schiff bases were characterized by the presence of the imine or azomethine (–C=N–) group. This review focused on some synthesis and biological activities of Schiff bases. From this review, it can be concluded that Schiff bases especially Schiff bases-heterocyclic moiety conjugates display a wide range of pharmacological activities. For that, Schiff bases attracted increasing attention to the scientists for the synthesis of new derivatives for applications in medicinal and in industrial field.

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72

Revolutionizing Applications: A Comprehensive Review of Schiff Base Nanoparticles at the Nanoscopic Scale

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Abstract
Nanotechnology has emerged as a transformative field with the potential to revolutionize various scientific and technological domains. This chapter delves into the nanoscopic marvels of Schiff base nanoparticles and their applications in advanced technologies. Schiff bases, known for their versatile coordination chemistry, have been harnessed to engineer nanoparticles with unique properties and functionalities. The exploration of these nanoscale wonders encompasses synthesis methodologies, characterization techniques, and their diverse applications in fields such as catalysis, drug delivery, sensing, and imaging. The chapter discusses the tailored design of Schiff base nanoparticles to achieve enhanced performance, stability, and selectivity in various applications. Moreover, it highlights the potential impact of these nanomaterials on advancing technologies and offers insights into future directions for research and development in this rapidly evolving field. The intricate interplay between molecular design, synthesis strategies, and applications underscores the significance of Schiff base nanoparticles as promising candidates for addressing contemporary challenges in nanotechnology.
Keywords: Schiff base nanoparticles, catalysis, drug delivery, nanotechnology.

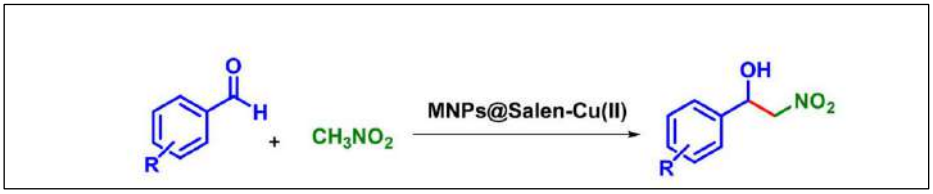
1. Introduction

The imine (-C=N-) functional group that results from the interaction of the amine amino group with the aldehyde or ketone carbonyl group defines the Schiff bases class of chemical compounds [1].The imine functionality of Schiff bases confers significant chemical and biological features, enabling these molecules to coordinate and complexate with metal ions in a variety of chemistry-related domains [2].Schiff base compounds can function as ligands to produce transition metal Schiff base complexes because of the imine group [3] . Additionally, the imine group (>C = N −) of SB ligands stabilizes the nanoparticles by forming bonds with them [4]. The term nanotechnology was first used in 1974 by Japanese scientist Norio Taniguchi and is considered a marvel of science, engineering, and technology [5-7].The word "nano" comes from the Greek "nanos," which means "small" (10^{-9} m). Nanoparticles (NPs) are essentially very small particulates that range in size from 1 to 100 nm [8].A higher level of the NPs is ensured by the surface modification, increasing their potential in the disciplines of analysis, electro analytical, catalysis, and biology. SB modified NPs are applied as biosensor, adsorbent, electro catalysis, catalytic dye degradation, and oxidation of different of various organic compounds [9-14].This chapter delves into the intricate realm of Schiff base nanoparticles, investigating their unique properties and potential applications in various advanced fields.

2. Schiff base complex as a heterogeneous catalyst:

A Cu(II)-Schiff base complex supported on functionalized Fe_3O_4 magnetic nanoparticles (MNPs@Salen-Cu(II)) was firstly prepared by the refluxing it in the toluene solvent for two days. Further this was stirred in ethanol at room temperature with the addition of benzaldehyde and nitromethane. These nanoparticles were employed as effective catalysts in the manufacture of derivatives of nitroaldol through the reaction of nitromethane with aldehydes (Scheme 1). The reaction benefits include selectivity to products, recyclability of the catalysts, simplicity

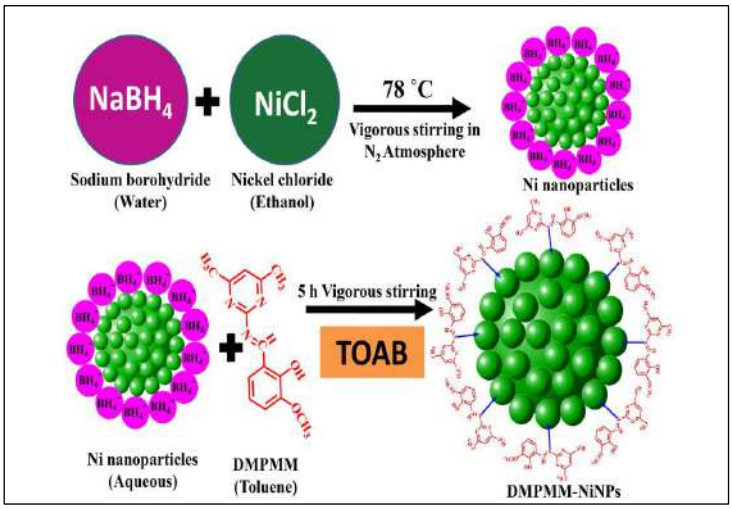
in workup, facile separation, cleanliness, and eco-friendliness. Using VSM, SEM, FT-IR, 1H NMR, XRD, TGA, and EDX, the produced catalysts were characterized. Using an external magnet, the nanocatalyst may be easily extracted from the reaction mixture and reused 14 times without experiencing a substantial reduction in catalytic activity. Research on the catalyst's leaching revealed that the heterogeneous catalyst's active components do not leach [15].



Scheme 1. Synthesis of nitroaldols by the MNPs@Salen-Cu(II)

3. Exploring the Multifaceted Applications of Nickel Nanoparticles Stabilized by Schiff Base Ligands:

Paulraj Adwin Jose et al. synthesized nickel nanoparticles stabilized by Schiff base ligands derived from pyrimidine derivatives and are verified by using spectroscopic and microscopic, SEM and TEM techniques (Scheme 2). The synthesized compounds exhibited strong DNA binding capability and binding through groove mode. The produced compounds enhanced DNA denaturation and the BSA binding investigations demonstrated the compound's strong BSA interaction. The DMPMM and DMPMM-NiNPs were the subject of antimicrobial investigations using the Agar-Agar well diffusion method. The results of anticancer experiments verified that the produced DMPMM-NiNPs had a specific characteristic of interacting with cancer cells as opposed to normal cells. However the activity rose to a level above that of regular cisplatin when it was capped with metal nanoparticles. The results of tests on antioxidant scavenging demonstrated the strong antioxidant activity of DMPMM-NiNPs [16].

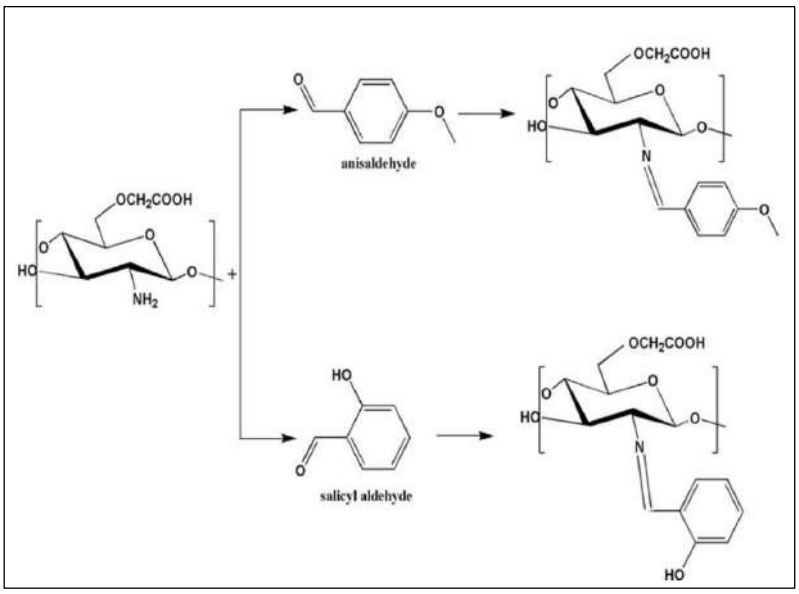


Scheme 2. Synthesis of Schiff base ligand capped nickel nanoparticles (DMPMM-NiNPs).

4. Schiff-Bases with Anisaldehyde or Salicylaldehyde in the Presence of Silver Nanoparticles:

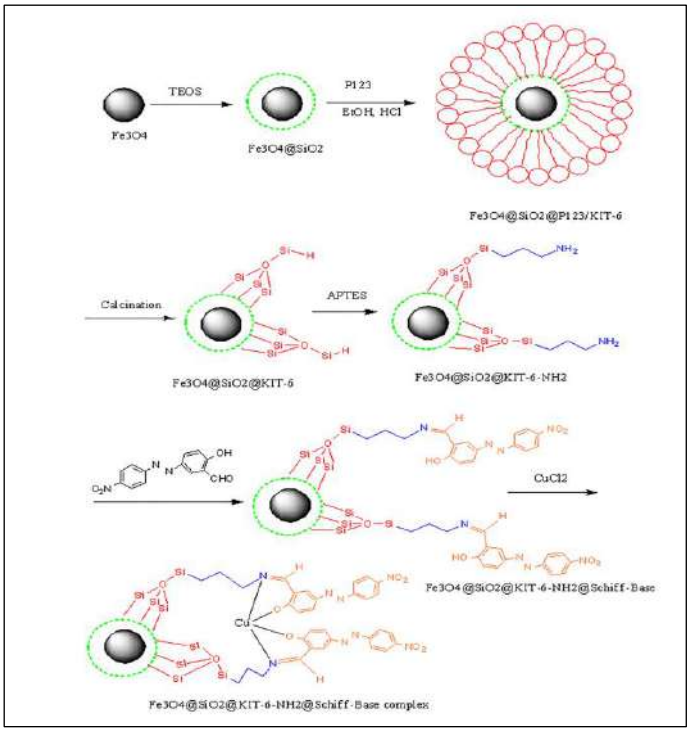
Carboxymethyl chitosan-Schiff-bases (CMCs-SB) of anisaldehyde or salicylaldehyde in the absence/presence of silver nanoparticles; with different weight ratios of $AgNO_3$ (2 and 5% by weight) were prepared by Reham A. Abdel-Monem et al. (Scheme 3) and evaluated as materials with antibacterial efficiencies. The material is characterized by FTIR, SEM, TEM, TGA.The two carboxymethyl chitosan Schiff-bases nanocomposites were found to exhibit inhibitory power against the growth of both Gram +ve and Gram -ve types of bacteria. The antibacterial efficiency of salicylaldehyde/CMCs-SB/AgNPs is higher than that of anisaldehyde/CMCs-SB/AgNPs. The human hepatocellular carcinoma cell line (HEPG2) and

the breast adenocarcinoma (MCF7) were used to test the cytotoxicity of the produced CMC Schiff bases in the presence and absence of AgNPs (2 and 5%). The findings demonstrated that adding AgNPs at weight ratios of 2 and 5 % enhanced the anticancer activity of the produced Schiff bases [17].



Scheme 3. Schematic diagram for the reaction of CMCs with anisaldehyde or salicyladehyde.

Leila Zare Fekri et al. synthesized a copper/Schiff base complex immobilized on amine-functionalized silica MMNPs (Scheme 4). Product is characterized by SEM, TEM, TGA and VSM analysis. The synthesized product is an effective catalyst in a multicomponent reaction involving amine, thioglycolic acid, and aldehyde while stirring. This nanoparticle is a novel mix of organic and inorganic materials. The key benefits of this catalytic process include waste reduction, good selectivity, easy separation and recycling of the magnetic catalyst, outstanding product yields, and low operating complexity. Additionally, this new route is affordable and safe for the environment [18].

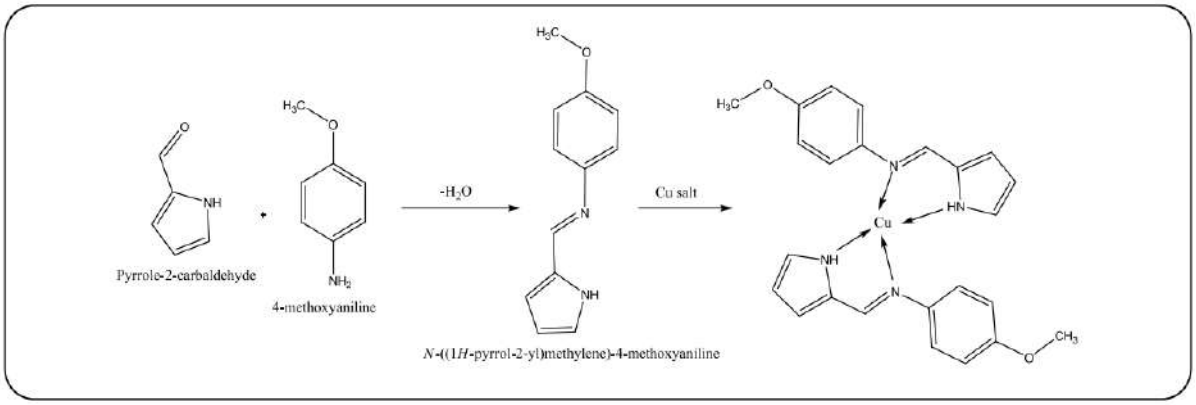


Scheme.4 Synthesis of Fe3O4@SiO2@KIT-6-NH2@Schiff base complex

5. Exploring Anticancer Potential through DNA Binding by Zn(II) Complex with Schiff Base Ligand:

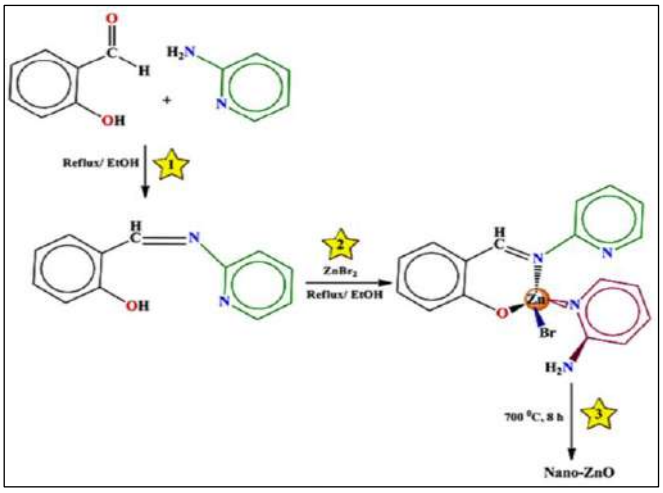
The study involves the synthesis of biologically potent Pt (II) metal ion complexes, characterized by a proposed square planar environment through various physicochemical investigations. These complexes exhibit higher antimicrobial activity compared to the original ligands and demonstrate a strong ability to cleave DNA via the oxidative nuclease pathway, confirmed by band tailing in the DNA spectrum. Additionally, the compounds show significant in vitro anticancer activity against human breast cancer (MCF-7) cell lines, with results compared to the standard drug Cisplatin. The Pt (II) complex induces DNA damage, as evidenced by increased cell cycle depletion of S and G2/M at various concentrations, leading to G1 phase arrest. A notable rise in sub-G1 cells indicates that the complex causes sufficiently high DNA damage, resulting in a large number of cells undergoing apoptosis [19].

Charles, A. et al. synthesized the ZnO film's polycrystalline nature, with its hexagonal wurtzite structure and (002) preferred orientation (Scheme 5). The compound is characterized by Atomic force microscopy (AFM), optical research, and X-ray diffraction (XRD). It was calculated that the grain size was in the nm range. The direct bandgap value of 3.2 eV in the produced films is in close agreement with the stated value of 3.37 eV found in literature. The characterisation studies verify that the deposited ZnO thin films are suitable for use in solar cells and optoelectronic devices [20].



Scheme 5: Synthesis of N-((1H-pyrrol-2-yl)methylene)-4-methoxyaniline Schiff base(PMMA) and its copper complex $[Cu(PMMA)_2]Cl_2.2H_2O$.

A novel compound of Zn(II) was synthesized and characterized using a metal with a molar ratio of 1:2 and a Schiff base ligand by Masumeh Galini et al. They used FT-IR, 1H-NMR, UV-Vis X-ray data to determine the structure of the synthesized compound. Furthermore, ZnO nanoparticles of [ZnL(2-aminopyridine)Br] using the combustion synthesis method was created Using FESEM, TEM, FT-IR, and XRD, the shape and crystalline structure of the produced zinc oxide nanoparticles were examined. Additionally, it was shown through the use of molecular docking techniques that the Zn(II) complex binds to the DNA helix's minor groove. [ZnL(2-aminopyridine)Br] will function as a tyrosine kinase inhibitor to treat cancer by blocking the receptor for the epidermal growth factor [21].



Scheme 6. Synthetic procedure for the preparation of Schiff base ligand and complex (2:1) and protocol of ZnO nanoparticles.

6. Conclusions

In conclusion, the exploration of Schiff Base Nanoparticles in this review highlights their remarkable potential for advanced applications at the nanoscopic level. The synthesis and characterization of these nanoparticles, with a focus on their unique properties, have paved the way for diverse applications in various fields. From enhanced antimicrobial activity and DNA cleavage capabilities to potent in vitro anticancer effects, Schiff Base Nanoparticles emerge as versatile candidates for innovative biomedical and materials science applications. As we delve into the intricacies of their physicochemical properties and biological activities, it becomes evident that Schiff Base Nanoparticles offer a promising avenue for addressing complex challenges in medicine, materials science, and beyond. The observed cell cycle depletion, G1 phase arrest, and induction of apoptosis underscore their potential as impactful agents in cancer therapeutics. The integration of Schiff Base Nanoparticles into the realm of nanotechnology signifies a frontier in the ongoing pursuit of advanced materials with tailored functionalities. Further research and development in this area are essential to unlock the full spectrum of possibilities and overcome potential challenges. As we embark on this journey, the nanoscopic marvels of Schiff Base Nanoparticles hold immense promise for shaping the future of advanced applications, offering unprecedented solutions for a myriad of scientific and technological endeavors.

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73

Screening Of Antioxidant Property Present In Psidium Guajava Linn

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Abstract:
Psidium guajava(Linn) is a member of Myrtaceae family, is a common tropical plant with a long history of traditional usage. Psidium guajava have been reported to possess variety of biology activity. Antioxidants both are natural and man-made substance that protects our cell from free radical. In present study we find out the antioxidant and phytochemical property of and water extract of Psidium guajava leaves by using DPPH as a free radical scavenger and colorimeter. The activity was evaluated by the decrease in absorbance as the result of DPPH colour change from purple to yellow. The higher the sample concentration used, the stronger was the free radical-scavenging effect. From this study we found that the Psidium guajava (linn) has good Antioxidant property. This study revealed that guava leaf extracts comprise effective potential source of natural antioxidants.

Key word: Psidium guajava leaves antioxidant property, DPPH.

Introduction

The guava is a small tree with tortuous branches and a smooth trunk. The fruit is a berry with a fleshy yellow or pink pulp and many seeds near the center. Many different varieties have been developed that vary in colour, size and in shape from round to ovoid to pear – shaped. The guava (*Psidium guajava* L.) tree , belonging to the Myrtaceae family, is a very unique and traditional plant which is grown due to its diverse medicinal and nutritive properties. Guava has been grown and utilized as an important fruit in tropical areas like India, Indonesia, Pakistan, Bangladesh, and South America. Different parts of the guava tree, i.e., roots, leaves, bark, stem, and fruits, have been employed for treating stomachache, diabetes, diarrhea, and other health ailments in many countries. Guava leaves (*Psidii guajavae folium*; GL) are dark green, elliptical, oval, and characterized by their obtuse-type apex. Guava leaves, along with the pulp and seeds, are used to treat certain respiratory and gastrointestinal disorders, and to increase platelets in patients suffering from dengue fever. GLs are also widely used for their antispasmodic, cough sedative, anti-inflammatory, antidiarrheic, antihypertension, antiobesity, and antidiabetic properties. Studies on animal models have also established the role of GL isolates as potent antitumor, anticancer, and cytotoxic agents.

Material and method:

The guava leaves were collected and shade dried at room temperature and coarsely powdered using an electric grinder. The coarse powdered materials of leaves were kept in the airtight polythene bag and stored in dry place. The powdered guava leaves were then extracted in distilled water.

Solvent extraction

Preparation of Aqueous extract of guava leaves.

Aqueous extracts of powdered guava leaves was prepared by boiling method. About 10 gram of powder of guava leaves was taken in 50 gram of distilled water and was warmed for about 10 min, and solution was then allowed to cool and filtered through a filter paper. The filtrate then was used for studying the antioxidant activity.

Phytochemical investigation of psidium guajava,linn.

Sr. no	Constituent	Aqueous Extract
1	Carbohydrate	+
2	Tannins	+
3	Saponins	-
4	Flavonoids	+
5	Alkaloids	-
6	Phenols	+
7	Glycosides	+
8	Proteins	-
9	Sterols	+
10	Anthocyanin	-

Study of qualitative antioxidant activity of psidium guajava linn.

Freshly prepared 0.02% of DPPH solution in ethanol was prepared. Single of Aqueous extract of guava leaves was taken on TLC plates, after drying the spots the TLC plates were dipped in DPPH solution and tested for Antioxidant activity.

The aqueous extract of guava showed prominent bleaching of purple colour of DPPH indicating that it has Antioxidant activity.

Qualitative antioxidant activity shown by aqueous extract of Psidium guajava.



Before DPPH.



After DPPH

STUDY OF ANTIOXIDANT ACTIVITY BY DPPH

The antioxidant activity of aqueous extract of guava leaves was assessed on the basis of radical scavenging effect of the stable 1,1- diphenyl 2- picrylhydrazyl (DPPH). The diluted working solutions of the test plant extract was prepared in water. 0.02% DPPH was prepared in ethanol 2 ml of solution having increasing concentration of guava extract, and optical density was measured at 517nm using colorimeter. A blank reading of DPPH was also recorded and % inhibition was calculated using the formula given below.

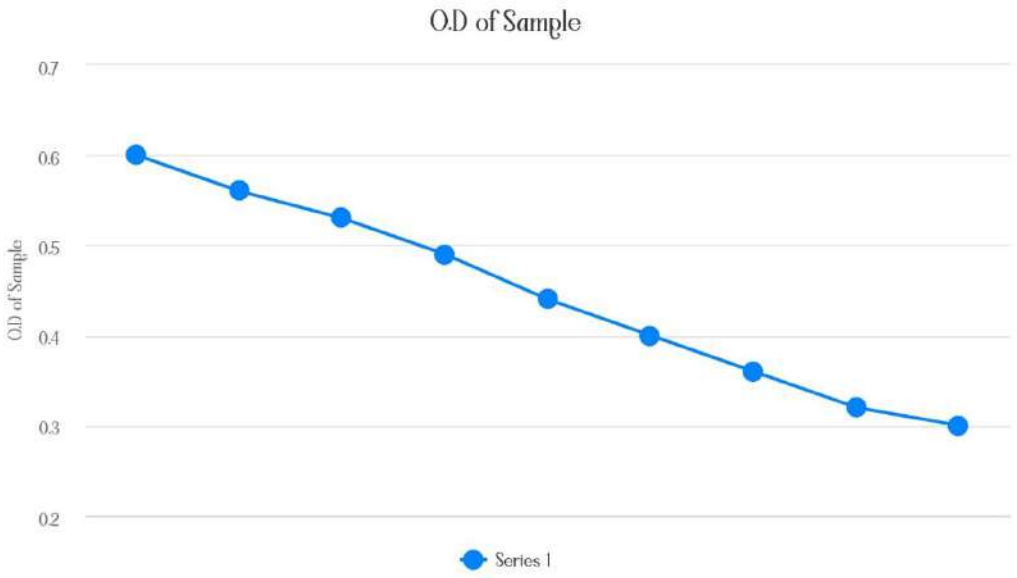
$$\text{Percentage (\%) Inhibition of DPPH (\%AA)} = \frac{A-B}{A} \times 100$$

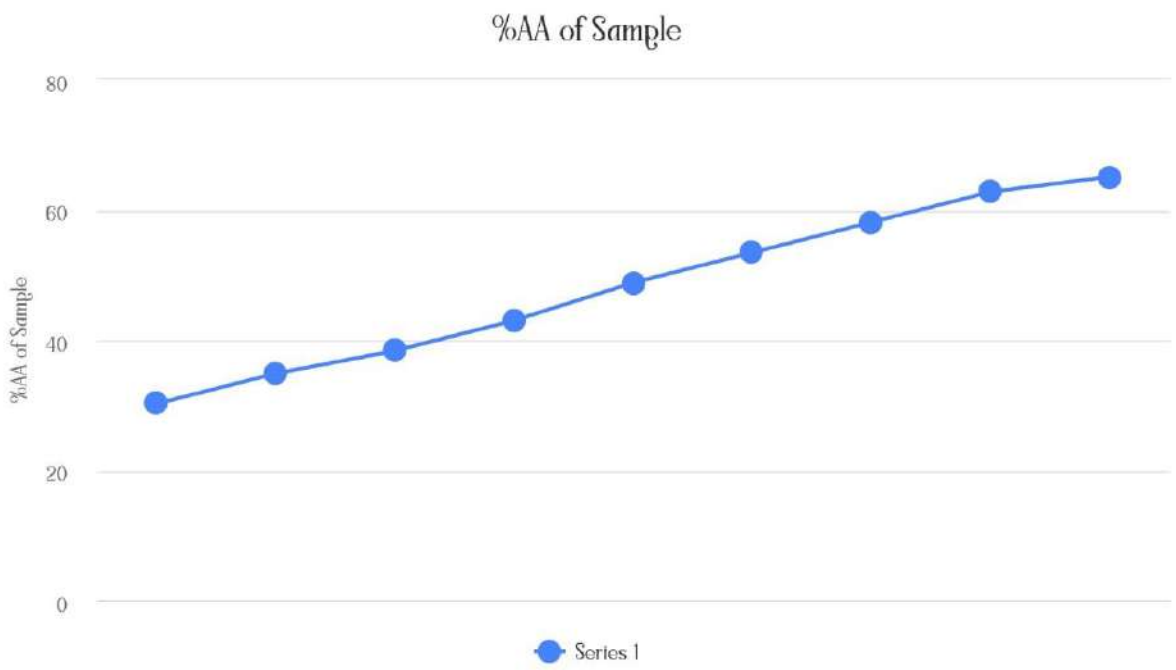
Where, A = Blank O.D of DPPH
B = O.D of sample solution.
From this we can calculate IC50 Value of each sample.
IC50 = Max (%AA) – 50% (Max - Min%AA)

Result and discussion:

Study on Quantitative Antioxidant activity of water extract of guajava leaves.
Table: **Optical density and percent Antioxidant of Aqueous extract of Guava.**

Concentration in mg/ml	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
O.D of sample	**0.60**	**0.56**	**0.53**	**0.49**	**0.44**	**0.40**	**0.36**	**0.32**	**0.30**
% AA	**30.23**	**34.88**	**38.37**	**43.02**	**48.83**	**53.48**	**58.13**	**62.79**	**65.11**





IC_{50} = Max (%AA) – 50 % (Max – Min % AA)
= 65.11 – ½ (65.11 – 30.23)
IC_{50} = 47.67

Conclusion:

The results obtained for the antioxidant assay by DPPH for water extract of leaves Psidium guajava plant were reported. The remarkable decrease in O.D value of the test plant samples were observed from the graph, showed antioxidant activity. The IC_{50} value for water extract of leaves of Psidium guajava was found to be 47.67mg/ml .

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74

In-Silico Prediction of Phytoconstituents From Solanum Indicum for Antiepileptic Activity

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ABSTRACT

Objective

A persistent, non-communicable brain disorder is epilepsy. Its distinctive characteristic is recurrent seizures. One or more parts of the body may experience partial or generalised seizures, which are short bursts of uncontrollable movement that can occasionally be followed by loss of consciousness and control over bowel or bladder function. Compounds found in medicinal plants have been the source of many conventional medications. *In-silico* testing of *Solanum indicum* phytoconstituents for antiepileptic efficacy was a part of our investigation.

Methods

Utilizing Discovery studio, molecular docking is done to assess the pattern of interaction between the phytoconstituents from the *Solanum indicum* plant and the crystal structure of the epilepsy proteins (PDB ID: 6O4L). Later, SwissADME and pkCSM were used to screen for toxicity as well as the pharmacokinetic profile.

Results

The docked results suggest that Solafuranone (-7.8 kcal/mol), Isofraxidin (-6.1 kcal/mol) for 6O4L macromolecule has best binding towards antiepileptic activity as compared to the standard (Acetazolamide) for 6O4L is -5.1 kcal/mol. Furthermore, pharmacokinetics and toxicity parameters were within acceptable limits according to ADMET studies.

Conclusion

Results from the binding potential of phytoconstituents aimed at antiepileptic activity were encouraging. It promotes the usage of *Solanum indicum* and offers crucial details on pharmaceutical research and clinical care.

1. INTRODUCTION

Solanum indicum, also known as Birhata, Badi Kateri, or Indian night shade, belongs to the Solanaceae family. It is a common upright undershrub in warmer parts of India, Asia, and Africa that grows up to 1.5 metres in height. Its height ranges from 0.30 to 1.8 metres. Nationally, 500–1000 MT are needed each year. The berries, leaves, roots, seeds, and stems of this plant have all been used in traditional medical systems to treat a wide range of ailments, including bronchitis, asthma, dry cough, rhinitis, dysuria, leucoderma, sexual dysfunction, insomnia, heart weakness, and pruritis.[1]

Solanum indicum, which is consumed as a vegetable in some regions of Africa, may prevent cardiovascular diseases. It was exciting to read the studies on how it may be used to treat hypertension. The extract's potent therapeutic and preventative benefits against hypertension may not have been possible without the presence of chlorogenic acids. The antihypertensive effect might be due to other components. The findings urge further research into the extract as a possible treatment for hypertension.[2]

However, there are few studies on the phytoconstituents of *Solanum indicum* for the antiepileptic activity. Thus, keeping the above information in view, the present investigation was designed to identify the potential phytochemicals of *Solanum indicum* against 6O4L using a molecular docking method.

2. MATERIALS AND METHODS

2.1. Platform for molecular docking

The computational docking study of all the phytoconstituents selected as ligands with antiepileptic activity as the target was performed using PyRx software.[3]

2.2. Protein preparation

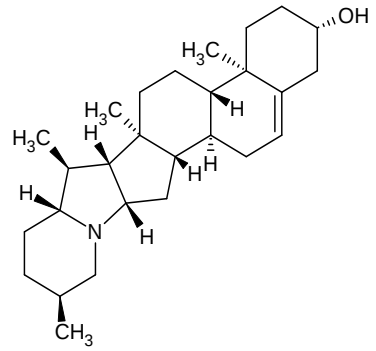
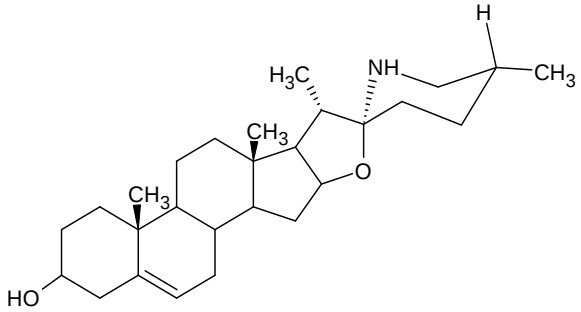
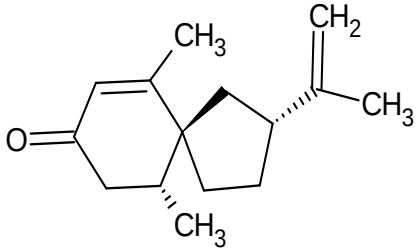
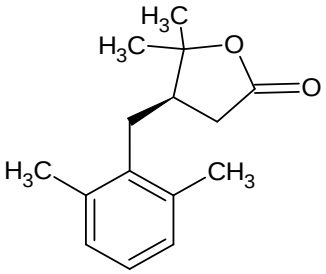
The macromolecule is 6O4L, *in silico* analysis of selected phytoconstituents was performed on the 1.85 Å crystal structure of antiepileptic macromolecule with inhibitor, (PDB ID: 6O4L, having resolution Resolution: 1.85 Å, R-Value Free: 0.220, R-Value Work: 0.174, R-Value Observed: 0.176), which was retrieved from the protein data bank (https://www.rcsb.org). 6O4L is classified as Crystal Structure of ALDH7A1 mutant E399D complexed with NAD all other molecules, such as co-crystallized water molecules, unwanted chains, and nonstandard residues, were deleted. Using Discovery studio.[4]

2.3. Mechanism of Action

6O4L: Aldehyde dehydrogenase 7A1 (ALDH7A1) is an enzyme that catabolizes lysine, and some loss-of-function mutations in this gene result in pyridoxine-dependent epilepsy (PDE). To understand how the mutations affect NAD+ binding, the crystal structures of the mutant enzymes in complex with NAD+ were examined. At the tested dose of NAD+, these alterations result in less active tetrameric ALDH7A1.[5]

2.4. Ligand preparation

The three-dimensional (3D) structures of all constituents were retrieved using Avogadro software from the PubChem database available on the NCBI website (https://pubchem.ncbi.nlm.nih.gov/). However, the drawing of geometrical 2D structure was performed using the ChemSketch program. The two-dimensional (2D) structures were transformed into 3D models using the Avogadro software and the ligand structures were saved in the PDB format. All the chemical structures are shown in Figure 1.

Solanidine 	Solasodine 
Solavetivone 	Solafuranone 

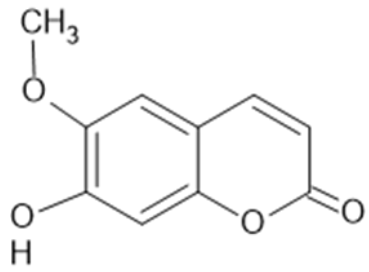
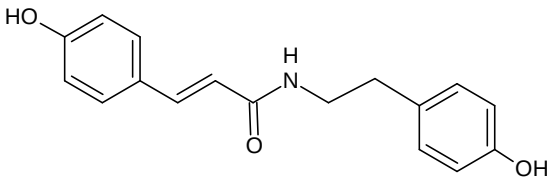
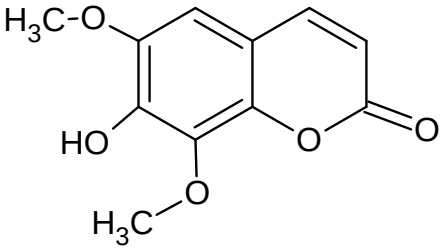
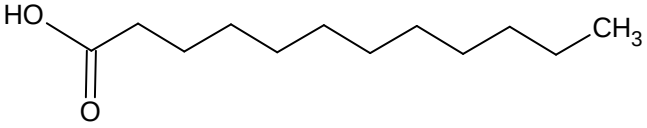
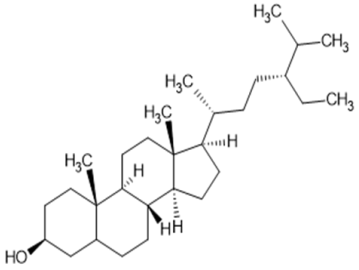
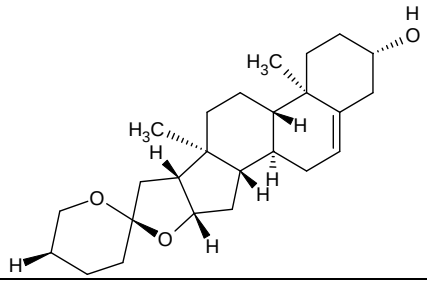
Scopoletin 	N-p-trans-Coumaroyltyramine 
Isofraxidin 	Lauric acid 
β-sitosterol 	Diosgenin 

Fig. 1**. Chemical structures of all selected phytoconstituents in the molecular docking studies**

2.5. Standard Preparation

The standard is prepared steps such as, the 2D structure of standard drug was made using chem sketch program, then the 2D structure was converted into 3D model using Avogadro Software, it was saved in PDB format.

By using PyRx molecular docking of Acetazolamide was done with 6O4L.

2.6. Molecular docking

Molecular docking evaluates the protein-ligand interactions and estimates the scoring function based on the geometry to predict the binding affinity of the ligand molecule[6,7]. We applied molecular docking studies to investigate the binding pattern of selected phytoconstituents (Figure 1) and the standard drug, along with the crystal structure of antiepileptic activity macromolecule (PDB ID: 6O4L). The molecular docking study was performed using PyRx software, Binding affinity was explored using the Vina wizard tool. The final results were analysed and visualized using Discovery Studio 2020 Client [8], with bound ligands as the standard. Visualization of protein ligand interaction reflects the number of interactions and active residues responsible for significant binding at the active site of the target enzyme.

2.7. Absorption, distribution, metabolism, and excretion (ADME) and toxicity prediction

The selected phytoconstituents and standard drug were further checked for drug-likeness properties according to Lipinski's rule. During drug development, it is necessary to predict the tolerability of phytochemicals before being ingested by humans and animal models.

The pharmacokinetic profile (ADME) and toxicity predictions of ligands were conducted using SwissADME (http://www.swissadme.ch) and pkCSM (an online server database predicting small-molecule pharmacokinetic properties using graph-based signatures, (http://biosig.unimelb.edu.au/pkcsm/prediction). To analyse the toxicological properties of ligands, Simplified Molecular Input Line Entry System (SMILES) notations or PDB files were uploaded, followed by selecting the required models for generating numerous information about structure-related effects[9,10].

3. RESULT AND DISCUSSION

The present study aimed to explore the inhibitory potential of the phytoconstituents present in *Solanum indicum* targeting antiepileptic activity. In this study, we performed molecular docking studies of all phytoconstituents found in *Solanum indicum* using AutoDock Vina, followed by a study of interacting amino acid residues and their influence on the inhibitory potentials of the active constituents. Selected phytoconstituents showing the best fit were further evaluated for absorption, distribution, metabolism, excretion, and toxicological (ADMET) properties using SwissADME and pkCSM servers.

3.1 Molecular docking

The docking scores and binding energies of all chemical constituents of *Solanum indicum* targeting antiepileptic activity (PDB ID: 6O4L) and binding interactions with amino acid residues are presented in Table 1 respectively.

Table 1**. Binding interaction of ligands from *Solanum indicum* targeting antiepileptic activity (PDB ID:6O4L)**

Sr. No.	Chemical constituent	PubChem ID	Docking Score
			6O4L
1.	Solanidine	65727	-10.0
2.	Solasodine	5250	-9.0
3.	Solavetivone	442399	-7.3
4.	Solafuranone	11107208	-7.8
5.	Scopoletin	5280460	-6.5
6.	N-p-trans-Coumaroyltyramine	5372945	-6.7
7.	Isofraxidin	5318565	-6.1
8.	Lauric acid	3893	-3.7
9.	β-sitosterol	222284	-7.1
10.	Diosgenin	99474	-8.1
Standard Drug			
11	Acetazolamide	1986	-5.1

The binding affinities of phytoconstituents ranged from –10.0 to -3.7 kcal/mol. From the docked results, it is evident that the compounds, Solanidine exhibit the most favourable binding affinity (−10.0 kcal/mol) in complex with selected macromolecules (PDB ID: 6O4L) as compared to other docked compounds i.e., Solsodine (-9.0 kcal/mol), Diosgenin (-8.1 kcal/mol), Solafuranone (−7.8. kcal/mol), Solavetivone (−7.3 kcal/mol), Beta sitosterol (-7.1 kcal/mol), N-p-trans-Coumaroyltyramine (−6.7 kcal/mol), Scopoletin (−6.5 kcal/mol), Isofraxidin (−6.1 kcal/mol), Lauric acid (−3.7 kcal/mol). Visual examination of the computationally docked optimal binding poses of phytoconstituents on selected macromolecules (i.e., 6O4L) revealed the significant involvement of various types of interactions, such as hydrogen bonding and hydrophobic interactions, including π–π stacking

and π–alkyl and alkyl interactions, in the stability of the binding of the phytoconstituents to 6O4L.

The binding affinity of the standard (Acetazolamide) for 6O4L is -5.1 kcal/mol.

3.1.1. Solafuranone, 6O4L

The number of intermolecular hydrogen bonds, the binding energy of ligand 6O4L stable complexes, and the number of nearest amino acid residues were also determined for selected compound Solafuranone All synthesized derivatives formed complexes with target proteins. Analysis of interactions of the 6O4L protein complex and ligand Solafuranone showed that the ligand molecule is oriented due to Conventional Hydrogen bond with THR A: 346 amino acid residue and Pi-Pi Stacked interaction with PHE A: 401 amino acid residue were found.

3.1.2. Isofraxidin, 6O4L

An analysis of the interactions between the 6O4L protein complex and the Isofraxidin ligand was also carried out, which showed that the ligand molecule is oriented due to conventional hydrogen bond with the ASP A: 399, THR A: 346, PHE A: 401 amino acid residue and Pi-Alkyl interaction with ALA A: 349 amino acid residue were found.

3.1.3. Acetazolamide, 6O4L

The binding affinity of the standard (Acetazolamide) for 6O4L is -5.1 kcal/mol. the interactions between the 6O4L protein complex and the Acetazolamide ligand was also carried out, which showed that the ligand molecule is oriented due to conventional hydrogen bond with the PHE A:166, THR A:164 amino acid residue, Carbon hydrogen bond with PRO A:193 amino acid residue, Pi-Sulfur interaction with PHE A:166 amino acid residue, Pi-Cation interaction with LYS A:190 and Pi-Alkyl interaction with ALA A:165, ALA A:192 amino acid residue were found.

Table No. 2. Interactions with amino acid residue.

Sr. No.	Molecule	Binding Energy (kcal/mol)	H bond	Main amino acid interactions	
				Pi-alkyl, alkyl, Pi-S/Pi-Pi, T shaped/halogen/unfavourable donor-donor interactions	Van der Waals interactions
1	Solanidine	-10.0	No interactions	ALA A:192, ALA A: 165, VAL A: 250	No interactions
2	Solasodine	-9.0	GLY A: 226	VAL A: 250, PRO A: 193	No interactions
3	Solavetivone	-7.3	ASN A: 379, ASN A: 46	TYR A: 41	No interactions
4	Solafuranone	-7.8	THR A: 346	PHE A: 401	No interactions
5	Scopoletin	-6.5	THR A: 164, PHE A: 401	CYS A: 302, ALA A: 165	No interactions
6	N-p-trans-Coumaroyltyramine	-6.7	SER A: 460	PHE A: 168, CYS A: 302, TRP A: 175, PHE A: 468	No interactions
7	Isofraxidin	-6.1	ASP A: 399, PHE	ALA A: 349	No interactions
8	Lauric acid	-3.7	PHE A: 292	PRO A: 288, LEU A: 285, PRO A: 458	No interactions
9	β-sitosterol	-7.1	No interactions	TRP A: 31, ALA A: 207, LYS A: 204, LYS A: 208, VAL A: 209, ALA A: 92	No interactions
10	Diosgenin	-8.1	ASN A: 379	TYR A: 41, PHE A: 166	No interactions

11	Acetazolamide	-5.1	THR A: 164, PHE A: 166, PRO A: 193	ALA A: 165, ALA A: 192, LYS A: 190	No interactions

3.2. ADMET study

Pharmacokinetic profile (ADME) and toxicity predictions of the ligands are important attentive parameters during the transformation of a molecule into a potent drug. In the present study, these parameters were assessed using SwissADME and pkCSM. The absorption potential and lipophilicity are characterized by the partition coefficient (Log *P*) and topological polar surface area (TPSA), respectively. For better penetration of a drug molecule into a cell membrane, the TPSA should be less than 140 Å. However, the value of Log *P* differs based on the drug target. The ideal Log *P* value for various drugs are as follows: oral and intestinal absorption, 1.35 − 1.80; sublingual absorption, > 5; and central nervous system (CNS)[11]. The aqueous solubility of ligands ideally ranges from − 6.5 to 0.5 [12], while the blood brain barrier (BBB) value ranges between − 3.0 and 1.2 [13]. In addition, non-substrate P-glycoprotein causes drug resistance [14].
In our study, all the selected ligands followed the TPSA parameter, P-glycoprotein non-inhibition, thereby showing good intestinal absorption and an acceptable range of BBB values. All the compounds showed aqueous solubility values within the range. Further, it was predicted that the selected ligands do not show AMES toxicity, hepatotoxicity, and skin sensitivity. In addition, it did not inhibit hERG-I (low risk of cardiac toxicity). Lipinski's rule violations, *T. pyriformis* toxicity, minnow toxicity, maximum tolerated dose, rat acute oral toxicity, and chronic toxicity are depicted in table.

Table 3. ADME and toxicity predicted profile of ligands with superior docking score

ADMET Properties	**Formula**	**MW (g/mol)**	**Log P**	**TPSA (Å²)**	**HB donor**	**Hb acceptor**	**Aqueous solubility (Log mol/L)**	**Human intestinal absorption (%)**	**Blood Brain Barrier**
Solanidine	$C_{27}H_{43}NO$	397.647	5.655	23.47 Å²	1	2	-4.927	92.975	0.695
Solasodine	$C_7H_{43}NO_2$	413.64	5.2869	41.49Å²	2	3	-3.809	92.324	0.035
Solavetivone	$C_{15}H_{22}O$	218.33	3.9042	17.07Å²	0	1	-4.615	95.873	0.635
Solafuranone	$C_{15}H_{20}O_2$	232.323	3.18764	26.30Å²	0	2	-3.551	95.523	0.206
Scopoletin	$C_{10}H_8O_4$	192.17	1.5072	59.67Å²	1	4	-2.504	95.277	-0.299
N-p-trans-Coumaroyltyramine	$C_{17}H_{17}NO_3$	283.327	2.4699	69.56Å²	3	3	-3.165	90.031	-0.552
Isofraxidin	$C_{11}H_{10}O_5$	222.196	1.5158	68.90Å²	1	5	-2.458	95.588	-0.377
Lauric acid	$C_{12}H_{24}O_2$	200.322	3.9919	37.30Å²	1	1	-4.181	93.379	0.057
β-sitosterol	$C_{29}H_{50}O$	414.718	8.0248	20.23Å²	1	1	-6.773	94.464	0.781
Diosgenin	$C_{27}H_{42}O_3$	414.63	5.7139	38.69Å²	1	3	-5.713	96.565	0.2
Acetazolamide	$C_4H_6N_4O_3S_2$	222.251	-0.8561	151.66 Å²	2	6	-2.428	59.043	-0.622

Table 3 Continued

ADMET Properties	P-glyco-protein substrate	Total clearance [Log mL/(min.kg)]	Bioavailability score score	AMES toxicity	Max tolerated dose [Log mg/(kg.d)]	hERG I inhibitor	hERG II inhibitor
Solanidine	YES	0.028	0.55	NO	-0.882	NO	YES
Solasodine	YES	0.09	0.55	NO	-0.375	NO	YES
Solavetivone	NO	1.225	0.55	NO	0.044	NO	NO
Solafuranone	NO	1.256	0.55	NO	0.526	NO	NO
Scopoletin	NO	0.73	0.55	NO	0.614	NO	NO
N-p-trans-Coumaroyltyramine	YES	0.265	0.55	NO	-0.213	NO	YES
Isofraxidin	NO	0.713	0.55	NO	0.56	NO	NO
Lauric acid	NO	1.623	0.85	NO	-0.34	NO	NO
β-sitosterol	NO	0.628	0.55	NO	-0.621	NO	YES
Diosgenin	NO	0.328	0.55	NO	-0.559	NO	YES
Acetazolamide	NO	-0.01	0.55	NO	1.263	NO	NO

Table 3 Continued

ADMET Properties	Acute oral rat toxicity. LD50(mol/kg)	Oral rat chronic toxicity (Log mg/kgbw/day)	Hepatotoxicity	Skin sensation	T.Pyriformis toxicity (Log µg/L)	Minnow toxicity (Log mmol/L)	Lipinski's rule Violation
Solanidine	2.596	1.334	YES	NO	0.378	-0.493	YES (1)
Solasodine	2.489	1.332	YES	NO	0.311	0.381	YES (1)
Solavetivone	1.643	1.19	NO	YES	1.453	0.874	YES (0)
Solafuranone	1.865	1.947	NO	YES	2.151	0.557	YES (0)
Scopoletin	1.95	1.378	NO	NO	0.516	1.614	YES (0)
N-p-trans-Coumaroyltyramine	2.17	1.271	NO	NO	1.008	1.514	YES (0)
Isofraxidin	2.326	1.825	NO	NO	0.431	1.862	YES (0)
Lauric acid	1.511	2.89	NO	YES	0.954	-0.084	YES (0)
β-sitosterol	2.552	0.855	NO	NO	0.43	-1.802	YES (1)
Diosgenin	1.921	1.452	NO	NO	0.399	0.247	YES (1)
Acetazolamide	2.292	2.143	NO	NO	0.239	2.895	YES (0)

3.3. Interaction of Standard Drug (Acetazolamide) with 6O4L

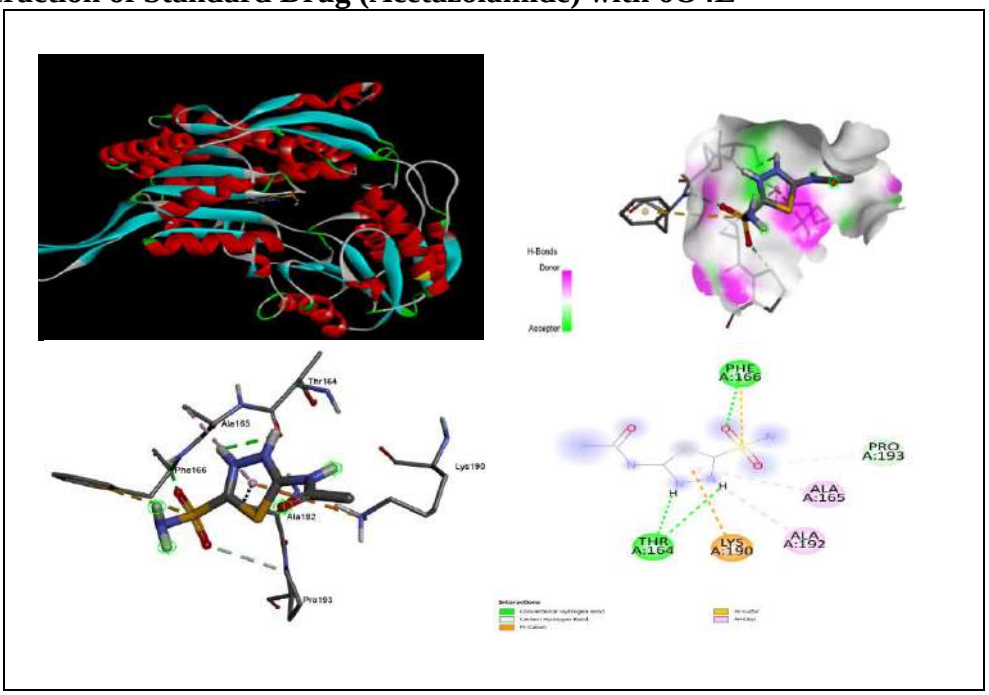
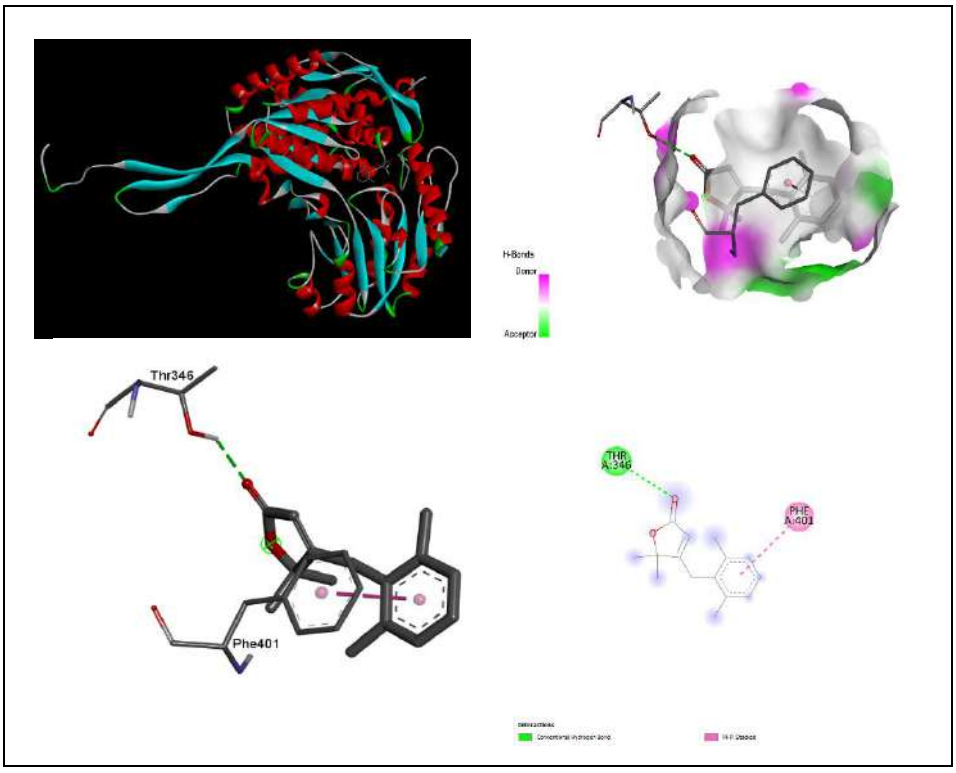


Fig. 2. Docking scores and binding interaction of Acetazolamide (PDB ID: 6O4L). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

3.4. Interactions of phytoconstituents with 6O4L

A.Solafuranone



B.Isofraxidin

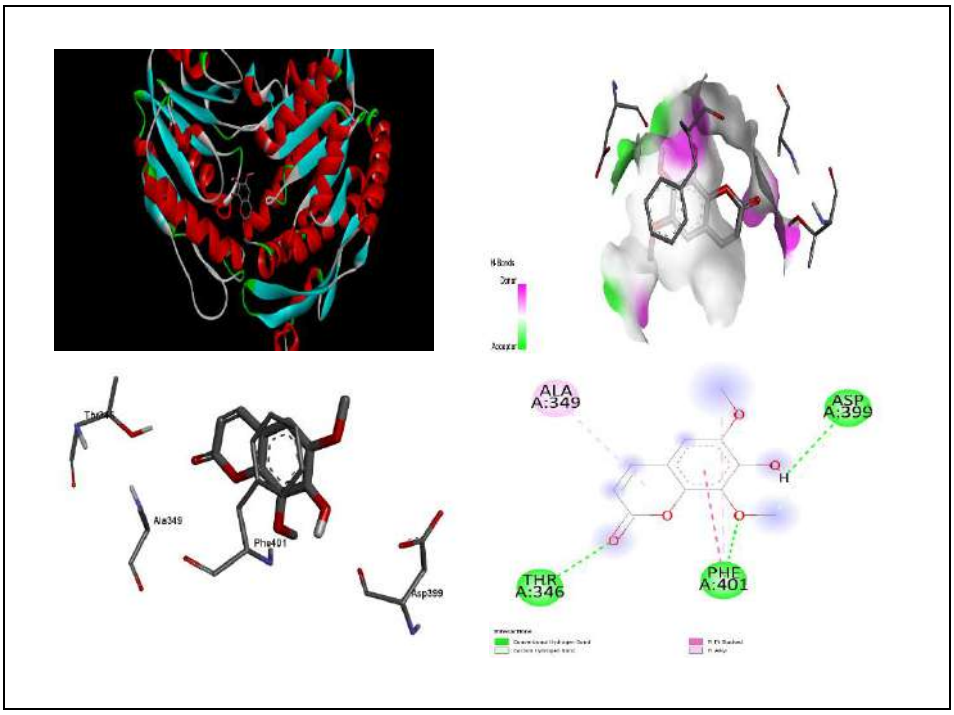


Fig. 3. Docking scores and binding interaction of phytoconstituents (PDB ID: 6O4L). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

3.5. Boiled Egg

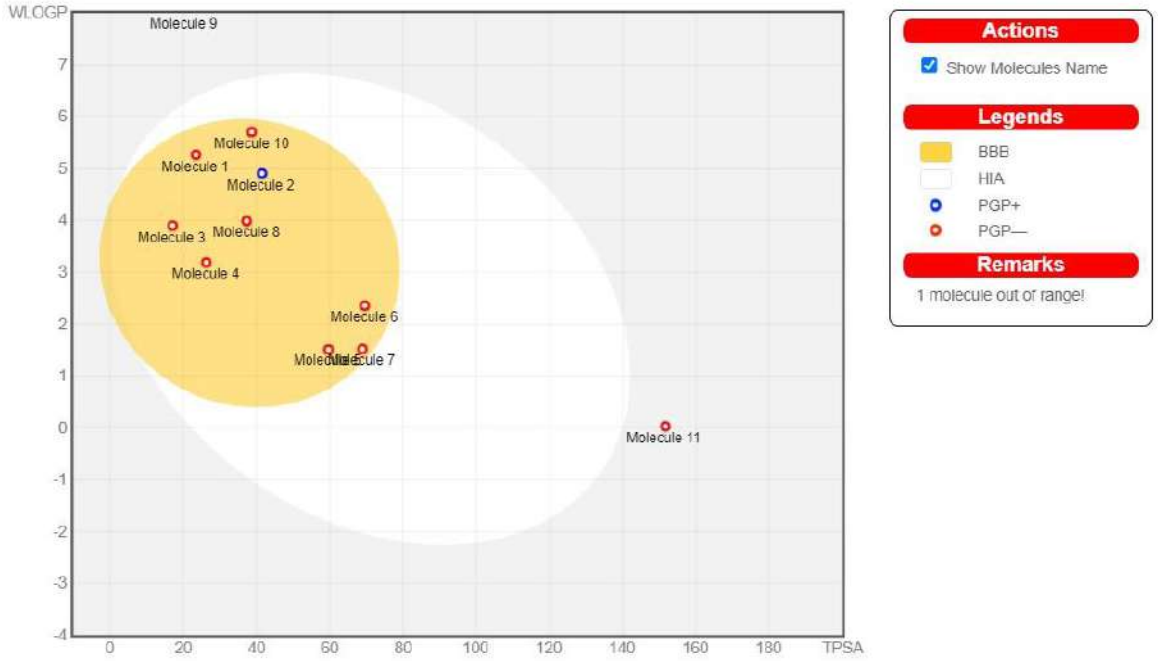


Fig no. 4. Combined Boiled Egg Diagram

Table no. 4. Name of molecules contained in Boiled Egg Diagram

MOLECULE NUMBER	MOLECULE NAME
1	Solanidine
2	Solasodine
3	Solavetivone
4	Solafuranone
5	Scopoletin
6	N-p-trans-Coumaroyltyramine
7	Isofraxidin
8	Lauric acid
9	β-sitosterol
10	Diosgenin
11	Acetazolammide

BOILED means Brain Or IntestinaL EstimateD permeation predictive model. The boiled egg diagram shows two regions white region and yellow region.
The white region is the physicochemical space of molecules with highest probability of being absorbed by the gastrointestinal tract, and the yellow region (yolk) is the physicochemical space of molecules with highest probability to permeate to the brain.
In addition, the points are coloured in blue if predicted as actively effluxed by P-gp (PGP+) and in red if predicted as non-substrate of P-gp (PGP-).

4. CONCLUSION

In this study, we have carried out an *in-silico* screening of the phytoconstituents of *Solanum indicum* plant. This study demonstrated the sixteen compounds from *Solanum indicum* plant, (Solanidine, Solasodine, Solavetivone, Solafuranone, Scopoletin, N-p-trans-Coumaroyltyramine, Isofraxidin, Lauric acid, β-sitosterol, Diosgenin). The selected phytocompounds showed docking scores ranging from –10.0 to −3.7 kcal/mol in 6O4L. Among all, Solafuranone and Isofraxidin gave the highest binding energy (−7.8 kcal/mol) and (−6.1 kcal/mol) in complex with 6O4L, whereas the reference compound, Acetazolamide showed a docking score with a binding energy of -5.1 kcal/mol. Furthermore, these ligands exhibited good ADMET properties. To summarize, phytoconstituents present in *Solanum indicum* possess strong effects against 6O4L and could be further evaluated for their antiepileptic effect, as well as for the development of alternative drugs with fewer side effects for the treatment of epilepsy.

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75

Development and Characterization of Piroxicam Matrix Based Transdermal Patch

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ABSTRACT:
The present study aims to develop and characterize matrix based transdermal patch for the treatment of dysmenorrhea using the drug Piroxicam, which is a non-steroidal anti-inflammatory drug of oxicam derivative. Matrix-based transdermal patches were prepared using a solvent casting method consisting of polymer (HPMC E5LV) and drug along with PEG 400 (plasticizer) and capsicum oleoresin (penetration enhancer) in a methanol and dichloromethane solution. All F_8 formulation batches prepared were evaluated and optimized. The result shows that the F_3 batch gives consistent results and all the evaluated parameters were within the standard limits. The in-vitro and ex-vivo %CDR of the optimized F_3 batch was found to be 98.76% and 97.65% respectively which indicates that the permeability of the drug through the goat skin within the time period of 2 hours is less than that of the dialysis membrane.The research work concluded that piroxicam matrix based transdermal patch was successfully prepared and evaluated which can provide direct entry of the drug into systemic circulation for immediate action in 2 hours. Therefore, piroxicam matrix based transdermal patches can be used to safely deliver the drug for the treatment of dysmenorrhea while avoiding therapy associated side effects and with good patient compliance.

KEYWORDS: Dysmenorrhea, Piroxicam matrix based transdermal patch, Capsicum oleoresin, HPMC E5LV, PEG 400.

INTRODUCTION

Dysmenorrhea has a negative impact on social, academic, sporting and daily activities. It is the most common problem that can be seen in adolescent and young women all over the world. Worldwide statistics shows that 51% of adolescent girls suffer from dysmenorrhea. Dysmenorrhea can be treated by using non-steroidal anti-inflammatory drugs (NSAIDs). Piroxicam is a non-steroidal anti-inflammatory drug of the oxicam derivative that are used to relieve pain, stiffness, tenderness and swelling by preventing the production of endogenous prostaglandins. This results in inhibition of prostaglandin biosynthesis. It has a role as an analgesic, a COX1 inhibitor, a non-steroidal anti-inflammatory drug, antipyretic, etc. It is used in the treatment of certain inflammatory conditions like primary & secondary dysmenorrhea, rheumatoid and osteoarthritis and postoperative pain. The transdermal drug delivery system (TDDS) is a route of administration where in active ingredients are delivered across the skin for systemic distribution. Transdermal patch is one of the conventional forms of transdermal drug delivery system.TDD is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation. Therefore, this work is formulated and evaluated the piroxicam matrix based transdermal patch for the treatment of Dysmenorrhea.

Application of Transdermal Delivery System

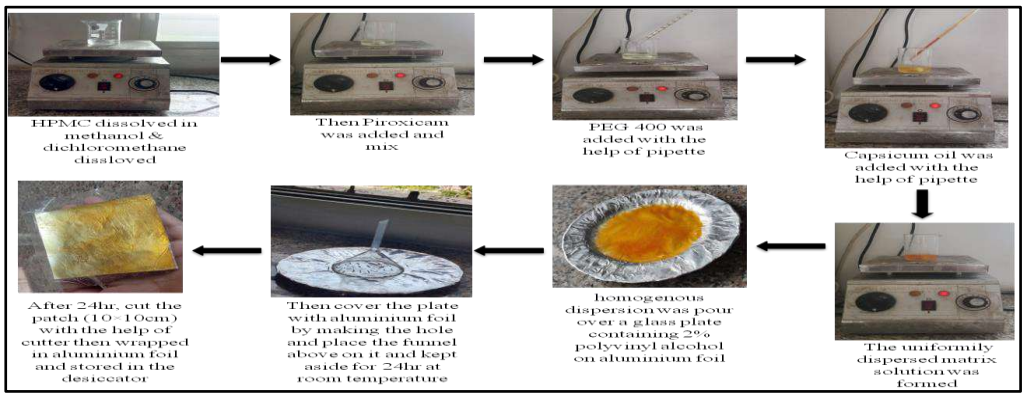
- Transdermal patches adhere to the skin as a way to deliver drugs. They provide a specific, predetermined dose of medication that is absorbed through the skin and penetrates into the bloodstream
- NSAIDs had been in first line of choice for transdermal drug delivery system for a long times due to their improved local effects and possibility to avoid the gastro-irritating effects.
- NSAIDs transdermal patches are most suitable techniques for reducing the adverse effects, increasing the bioavailability by avoiding first-pass hepatic metabolism, elevating the permeability of NSAIDs, and facilitating sustained release of drug for the longer duration of time.
- The drugs such as analgesic, antipyretic, antidepressant, antianginal and NSAIDs can be given by using transdermal drug delivery system.

MATERIALS AND METHODS

Chemicals

Piroxicam was purchased from Yarrow Chem Products, Mumbai, India. HPMC E5 LV was procured from Central Scientific Company, Nagpur, India. PEG 400 and methanol was procured from The Global Marketing, Nagpur, India and dichloromethane were procured from Genex Scientific Company, Nagpur, India. Capsicum oleoresin was purchased from Avi Naturals, Delhi, India. All other chemicals and reagents used in the study were of analytical grade.

Method of preparation of matrix based transdermal patch



RESULTS AND DISCUSSION

Evaluation of Transdermal patches

Physical appearance

The formulated patches were found to be clear, smooth, uniform, flexible and light yellow colour in their physical appearance as shown in figure



***In-vitro* diffusion cell study**

Formulation Code	Thickness (mm)±S.D	Weight Uniformity (mg) ± S.D	Folding Endurance ± S.D	% Moisture Content (%w/w) ± S.D	% Moisture Uptake (%w/w) ± S.D	Drug Content (%) ± S.D
F_1	0.690 ± 0.051	540.75 ± 0.88	7.67 ± 1.16	2.84 ± 0.57	6.6 ± 0.19	98.8 ± 0.45
F_2	0.554 ± 0.024	499.5 ± 0.75	6 ± 1	2.53 ± 0.2	4.25 ±	98.4 ±
F_3	**0.323 ± 0.007**	**301.12 ± 0.35**	**9 ± 1**	**2.24 ± 0.02**	**0.13**	**0.19**
F_4	0.648 ± 0.048	566 ± 0.92	5.67 ± 0.58	4.14 ± 0.31	5.2 ± 0.56	98.18 ± 0.33
F_5	0.544 ± 0.018	470.37 ± 0.74	6.33 ± 2.31	2.64 ± 0.19	4.6 ± 0.29	94.1 ± 0.70
F_6	0.615 ± 0.036	520.5 ± 0.80	8 ± 2	4.36 ± 0.04	5.95±0.37	95.8 ± 0.39
F_7	0.337 ± 0.008	355.75 ± 0.46	6.66 ± 1.53	2.45 ± 0.03	3.77 ± 0.27	97.8 ± 0.79
F_8	0.450 ± 0.009	388.62 ± 0.51	7.33 ± 1.52	3.03 ± 0.06	5.88 ± 0.20	98.6 ± 0.25

Figure 1: *In-Vitro* diffusion cell study for % Cumulative Drug Release

The % of drug release orders was as follows: $F_3 > F_1 > F_8 > F_2 > F_4 > F_7 > F_6 > F_5$. The formulation F_3 batch showed a better *in-vitro* drug release profile across the dialysis membrane when compared to the other formulations (figure 12). This might be attributed to the nature of the polymer; plasticizer and the permeation enhancer used. Thus formulation F_3 is considered an optimized formulation

***Ex-vivo* skin permeation study**

The F_3 batch ex-vivo skin permeation study was performed. The patch was exposure to the goat skin, 97.65 % of the drug was permeated and 98.76 % of the drug was permeated from in-vitro diffusion of optimized F_3 batch as shown in table 12. Thus, the amount of the drug permeated through the goat skin was less than the dialysis membrane. The graph (figure 13) of cumulative drug release, *ex-vivo* skin permeation and *in-vitro* cell study of an optimized batch (F_3)

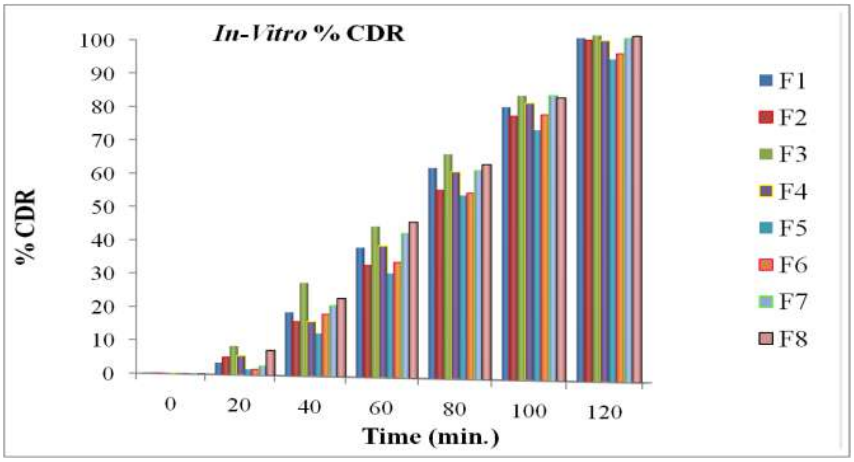


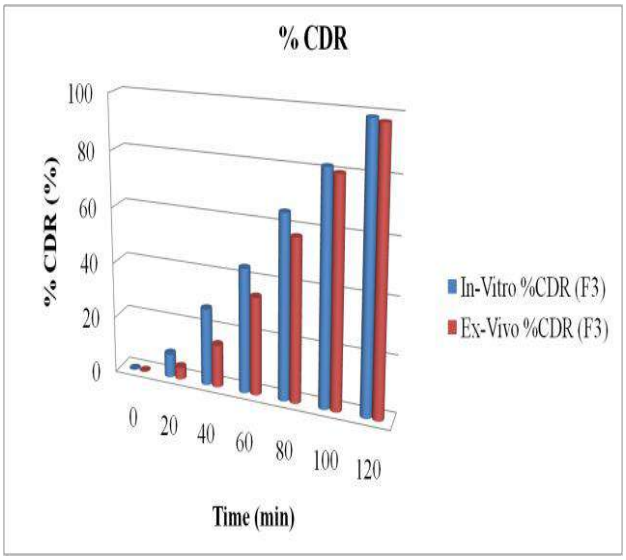
Figure 2: % Cumulative Drug Release *ex-vivo* skin permeation Vs *in-vitro* study of an optimized batch (F_3)

Sr. No.	Time (min.)	*In-Vitro* %CDR (F_3) (%)	*Ex-Vivo* %CDR (F_3) (%)
1	0	0	0
2	20	8.52 ± 1.16	4.25 ± 1.39
3	40	27.46 ± 1.75	15.12 ± 2.26
4	60	44.19 ± 3.47	34.69 ± 3.96
5	80	65.8 ± 5.34	57.40 ± 1.94
6	100	81.85 ± 5.29	80.06 ± 1.95
7	120	98.76 ± 0.57	97.65 ± 0.65

Stability study of optimized F_3 batch

Stability study was performed for optimized F_3 batch (piroxicam matrix based transdermal patch) was wrapped in aluminium foil by placing in the zip lock bag and kept in stability chambers at 40°C/75% RH for accelerated study of 6 months. Formulation was removed at each time point (0 day, 1 month, 3 month and 6 month) and evaluated for physical appearance, weight uniformity, thickness, folding endurance and drug contents. The in-vitro & ex-vivo permeation study were also performed. The stability study was completed as shown in table

Time (months)	Appearance	Thickness (mm)	Weight Uniformity (mg)	Folding Endurance	Drug Content (%)	*In-Vitro* %CDR (F_3)	*Ex-Vivo* %CDR (F_3)
0	Pale light yellow	0.323 ± 0.007	301.12 ± 0.35	9 ± 1	99.17 ± 0.19	98.76 ± 0.57	97.65 ± 0.65
1	Pale light yellow	0.320 ± 0.008	298 ± 0.39	10 ± 1.15	98.95 ± 0.35	98.35 ± 0.71	96.76 ± 0.61
3	Pale light yellow	0.324 ± 0.010	306.1 ± 0.1	12 ± 2.2	98.43 ± 0.5	98.12 ± 1.6	95.98 ± 1.5
6	Pale light yellow	0.319 ± 0.009	299.07 ± 0.37	10 ± 1.05	99 ± 1	98.54 ± 0.8	97 ± 1



CONCLUSION

It is concluded that piroxicam matrix based transdermal patch was successfully formulated and evaluated which may provides direct entry of the drug into the systemic circulation for immediate action in 2 hours. The identification of drug shows pure piroxicam. The prepared matrix based transdermal patch evaluation reveals that the F_3 batch is an optimized batch which shows good uniformity in the evaluation parameters of the patch. Such drugs delivery systems can be used to avoid side effects associated with therapy and safely deliver the drug for the treatment of dysmenorrhea with good patient compliance.

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76

Analytical Method Development and Validation of Antidiabetic Drugs

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ABSTRACT

The present study focuses on the analytical method development and validation of antidiabetic drugs by Uv-visible spectrophotometry and High-Performance Liquid Chromatography. Developing single analytical method is challenging task. A simple, rapid, precise and reliable method was developed for the estimation of bulk antidiabetic drugs. The estimation was carried out using an Inertsil-C18 BDS column (250 mm × 4.6 mm, 5 µm) and the mobile phase composed of methanol: H2O (80:20) at flow rate 1.0ml/min. Detection and Quantification were performed by Uv-visible detection at 230 nm. The retention time of metformin and dapagliflozin was found to be 3.08 and 3.87 minutes respectively. The validated method was successfully applied to the commercially available pharmaceutical dosage form, yielding good and reproducible results.

Keywords: Metformin and Dapagliflozin, Uv-visible spectrophotometry and High-Performance Liquid Chromatography

INTRODUCTION:

Metformin is a biguanide antihyperglycemic agent and first-line pharmacotherapy used in the management of Type II diabetes. Metformin is considered an antihyperglycemic drug because it lowers blood glucose concentrations in Type II diabetes without causing hypoglycemia. It is commonly described as an "insulin sensitizer", leading to a decrease in insulin resistance and a clinically significant reduction of plasma fasting insulin levels.

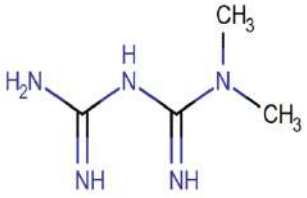


Fig.1

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and it was the first SLGT2 inhibitor to be approved. indicated for managing diabetes mellitus type 2. When combined with diet and exercise in adults, dapagliflozin helps to improve glycemic control by inhibiting glucose reabsorption in the proximal tubule of the nephron and causing glycosuria.

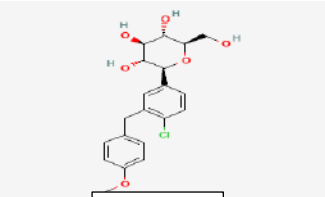


Fig2

Method

Selection of wavelength

Wavelength determination for HPLC analysis involved recording UV spectra (200-400 nm) for individual Metformin and Dapagliflozin solutions. UV spectrum of standard Metformin and Dapagliflozin was observed at 230 nm.

Chromatographic conditions

The developed method employs a reverse-phase C18 column, with a mobile phase consisting of Methanol: H2O in the ratio of 80:20 v/v. The mobile phase flows at a rate of 1.0 ml/min, and each injection involves 20µl of the sample. Detection was performed at a wavelength of 230 nm.

Preparation of Standard drug Solution of Metformin and Dapagliflozin

Accurately weighed quantity of 120 mg Metformin diluted to 10 ml of diluent and 24 mg of Dapagliflozin was dissolved in diluent and volume was made up to 100 ml mark by same to obtain 1000 µg/ml. Then further diluted to obtain 100 ppm stock solution. From standard stock solution pipette out 2 ml and dissolved in 20 ml of diluent to obtain 10 µg/ml of solution.

RESULT AND DISCUSSION

Method development

A reverse-phase HPLC method was developed with consideration for key system suitability parameters, including the resolution factor (Rs) between peaks, peak asymmetry (A), number of theoretical plates (N), run time, and cost-effectiveness. In conclusion, the developed method is deemed specific. System precision was evaluated through six replicate injections of the standards mixture at working concentration, revealing a % RSD (Relative Standard Deviation) less than 2 for peak area of both drugs. This signifies acceptable reproducibility and precision within the system.

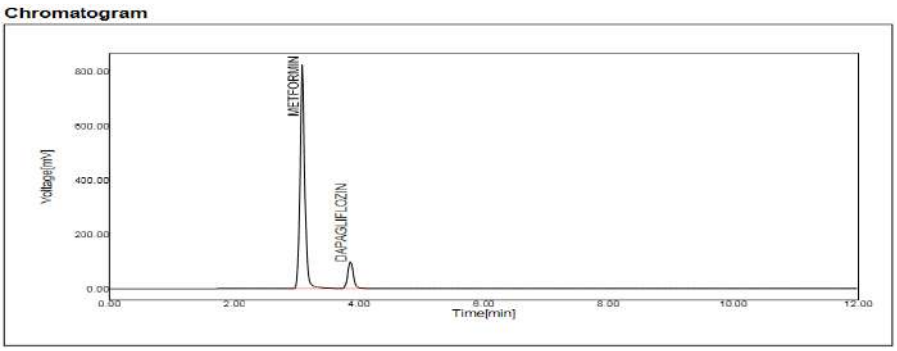


Fig4

Method validation

The HPLC method developed underwent validation following International Conference on Harmonization (ICH) guidelines. The validation included assessments for linearity, accuracy, system precision, intra-day precision, ruggedness, limit of detection (LOD), and limit of quantification (LOQ). Specificity was confirmed by observing peaks only in the standards and sample solutions at working concentrations, with no interference from the blank. The method is considered specific.

System precision was evaluated through six replicate injections of the standards solution at working concentration, showing % RSD (Relative Standard Deviation) less than 2 for peak area of both drugs, indicating acceptable reproducibility and precision.

Method precision was determined by assaying the sample under repeatability conditions (intraday precision) at working concentrations.

System suitability

System suitability is an essential pharmacopeial requirement utilized to assess the reproducibility of a chromatographic system, ensuring its adequacy for accurate analysis

In the study was assessed through recovery studies, involving the addition of standard drug solution to reanalyzed sample solutions at three concentrations: 80%, 100%, and 120% of the spiked levels. The accuracy was determined based on recovery studies conducted using the spiked method, covering the range of 80-120% of the labeled claim.

Linearity

Linearity in analytical methods indicates results directly proportional or following a defined mathematical transformation relative to analyte concentration within a specified range. Assessment involves analyzing samples across the claimed concentration range, creating a graph of area versus analyte concentration, and calculating percentage curve fittings to confirm linearity

Precision

Acceptance criteria require that the Relative Standard Deviation (RSD) should not exceed 2% for the test. The Standard Deviation (SD) and the Relative Standard Deviation (RSD) are calculated from the mean of five injections of the Standard solution and reported for evaluation.

Robustness

Robustness testing of the analytical method aimed to verify its stability against minor variations in optimized parameters. Small changes were introduced in factors such as flow rate, mobile phase composition, and wavelength. Specifically, variations of ±0.1 ml/min in flow rate, ±5 in mobile phase composition, and ±2 nm in wavelength were implemented. The robustness of the method was assessed by calculating the % RSD values to ensure the method's reliability despite these slight variations.

SUMMARY AND CONCLUSION

Name	Preparation	%Assay
1.0 ml/min	Preparation-1	100.27
	Preparation-2	98.86
0.9 ml/min	Preparation-1	98.95
	Preparation-2	99.08
	Mean	99.29
	SD	0.6595
	%RSD (NMT 2)	0.66

An RP-HPLC method was established and applied to pharmaceutical dosage forms for Metformin and Dapagliflozin. A validated simple reverse-phase liquid chromatographic method was developed. A UV-spectrophotometric method has been developed, demonstrating accurate results for estimating drugs in a mixture. The separation method utilized a mobile phase composed of Methanol, Water, and Trifluoroacetic acid in a ratio of 80:20. Detection was performed using UV–Visible SPD 20 A at 230 nm. The column employed was Hypersil BDS C18 (250 mm × 4.6 mm, 5µm), and the flow rate was set at 1 ml/min.

The retention times for Metformin and Dapagliflozin were determined as 3.08 and 3.87, respectively. The asymmetry factors or tailing factors of 1.17 and 1.10 suggested a symmetrical peak nature at ambient temperature with an injection volume of 20 µl. The number of theoretical plates was determined as 17196 and 15475, indicating the efficiency performance of the column. Linearity studies were conducted, and specified concentration levels were determined.

The method was validated according to ICH guidelines, demonstrating accuracy, precision, selectivity, and cost-effectiveness. With sharp and well-defined peaks, the method is suitable for the estimation of Metformin and Dapagliflozin in both bulk and pharmaceutical dosage forms.

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77

Synthesis of colloidal metal oxide using reverse micelle technique and its application in coupling reactions for Benzoxazole formation

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Abstract:
Metal oxides have profound applications in the various advanced technologies using its catalytic, gas sensing, optoelectronic, ceramic, piezoelectric properties. Physiochemical properties of metal oxides are tuned using various synthetic methods to synthesize particles of various shapes, sizes and geometries. Therefore, focus of the researchers and scientists is to prepare metal oxides nanoparticles using various synthetic routes of Chemical, physical and biological methods. But either these synthetic routes are complicated, energy intensive or producing nanoparticles having potent toxicity which can restrict its long-term use in the various applications and technologies. Potential toxicity of nanoparticles is due to its accumulation in vital organs of the body. Exposure to nanoparticles could trigger the production of reactive oxygen species which subsequently disturb the metabolism as well as damage proteins, enzymes, cell membranes and also DNA. Therefore, for sustainable development of nanotechnology use of nanoparticles in consumer products, environmental benign techniques for the synthesis of metal oxides are to be practiced. Colloidal metal oxides particles have shown promising results in this direction, as colloids are biocompatible in its synthetic ways as well as its application modes. Therefore, in this article, we have focused to prepare copper oxide and nickel oxide using some synthetic methods which successfully lead to synthesize colloidal metal oxides. Characterization of synthesized metal oxide is done for its shape, size, morphology using techniques such as SEM, XRD, FT-IR and BET. These metal oxides subsequently used for reactions which forms the basis of complicated reactions taking place in plant and animal body. These reactions are mainly coupling reactions involving C-N bond and C-O bond formation.

Key words: Metal oxide, nanotechnology, toxicity, reverse micelle, Coupling reactions, Benzoxazole

1. Introduction:

Metal ions are fundamental elements present in plants and animals. Their substantial role in biological systems was recognized a long time ago. They are essential for the maintenance of life and their absence can cause growth disorders, severe malfunction, carcinogenesis or death. They are protagonists as macro or microelements in several structural and functional roles, participating in many biochemical reactions, and arise in several forms. They participate in intra and inter cellular communications, in maintaining electrical charges and osmotic pressure, in photosynthesis and electron transfer processes, in the maintenance of pairing, stacking and the stability of nucleotide bases, and also in the regulation of DNA transcription. They contribute to the proper functioning of nerve cells, muscle cells, the brain and the heart, the transport of oxygen and in many other biological processes up to the point that we cannot even imagine a life without metals.[1]

Heterocyclic moieties play a significant role in the field of drug discovery. C−N and C−O bond formation reactions are the primary synthetic sequence for the generation of heterocyclic molecules. The generation of C−N and C−O bonds involves the use of mostly Pd or Cu

catalysts although other transition metal catalysts are also involved. However, in C−N and C−O bond formation reactions, several problems were faced such as catalytic systems containing costly ligands, lack of substrate scope, lots of waste generation, and high temperature conditions. So it is imperative to uncover new eco-friendly synthetic strategies which provides a short reaction time, tolerance for functional groups, and less waste production. [2, 8, 9]

Microbial organisms possess an incredible capability of fabricating extremely specialized inorganic nanostructures. These magnificent skills of the living creatures have caught the attention of many material scientists towards these biological systems to acquire knowledge and recuperate the skills for the precise formulation of nanostructures. Generally, synthesis of inorganic nanomaterials by living organism has been categorized as biologically controlled and biologically induced synthesis. Biologically controlled synthesis is well-known to occur naturally in a few organisms. During this type of synthesis, the organisms are able to modulate the particle size, composition and surface area of the produced particles. Though biologically controlled synthesis of metal oxide nanoparticles exhibits high control over the morphology and composition of the nanoparticles. [3,4]

The basic idea of the colloidal method is to limit particle growth. As the formation of very small crystals is thermodynamically unfavourable due to the high surface energy of such particles, nanosynthesis must be controlled by kinetics. To achieve this, surfactant molecules are used to limit particle growth. One method uses a non-polar solvent, leading to the formation of reversed micelles. In the polar core of the micelle, a minute amount of water is present in which precipitation of the nanocrystal takes place. The size of the micelles thus determines the size of the particles. [5,6]

Benzoxazoles are an important class of heterocyclic compound that are encountered in a number of natural products and are used in drug and agrochemical discoveries. As a consequence, much effort has been devoted not only to construct basic skeleton of benzoxazole molecules but also to prepare derivatives through C-O or C-N atom bond formation. Hence development of an efficient methodology for the preparation of benzoxazole and its derivatives has gained a lot of importance in current research. [10,11]

2. Synthesis and characterisation of MO:

Cuprous oxide (Cu_2O) is produced by chemical reduction of copper sulphate salts in water-in-oil microemulsion solution using $NaBH_4$ as a reductant. Water-in-oil (w/o) microemulsions also called reverse micelles are water pools stabilized by surfactants, dispersed in oil phase, that serves as nanoreactors in which nanoparticles form and serve in controlling the size of nanoparticles. The water pools being stabilized by the lipopeptidal surfactant act both as nanoreactors for the process reaction and prevent particle aggregations as the surfactants get adsorbed on the particle surfaces when the particle size approaches the water pool, resulting in fine and uniform particle size distribution. Colloidal particles were then supported on γ-Al_2O_3 are then dried in oven at 80^0C for an hour. Characterisation of this colloidal metal oxide is done by FTIR, SEM and XRD.

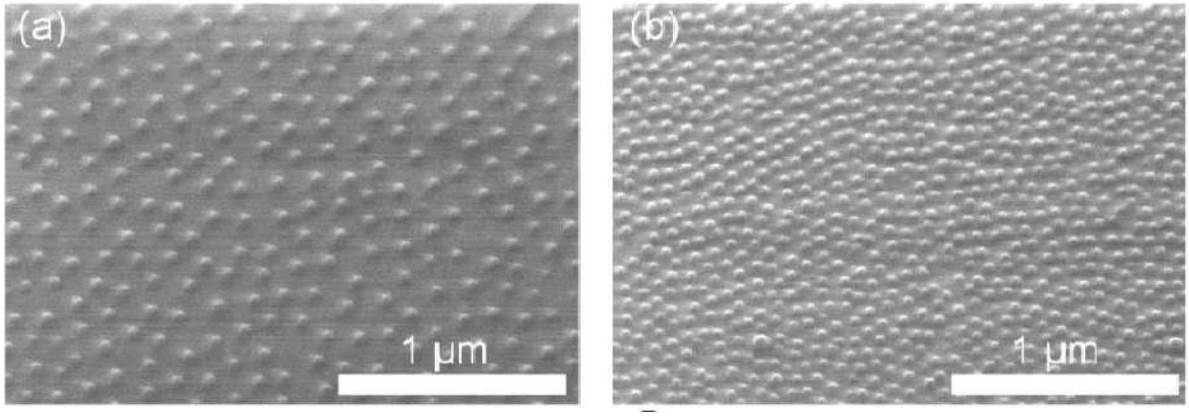


Figure 1 : SEM micrographs at different O/W ratio.

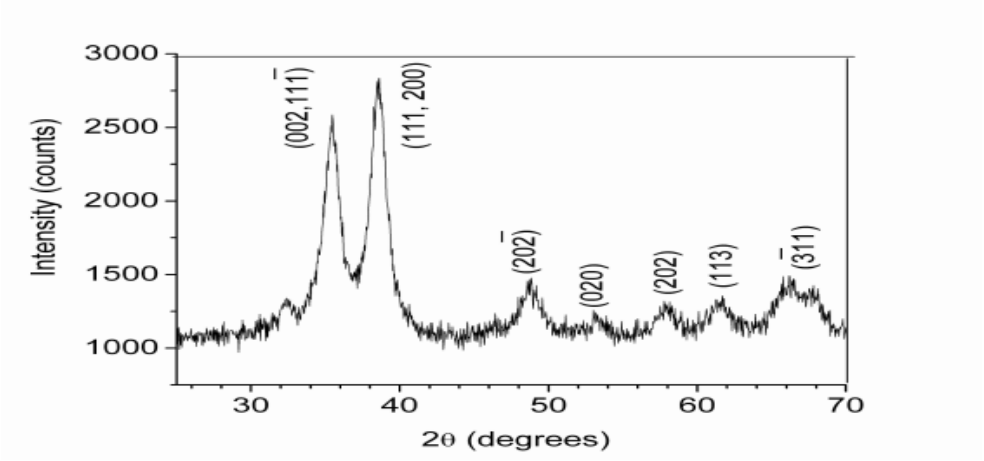


Figure 2: XRD

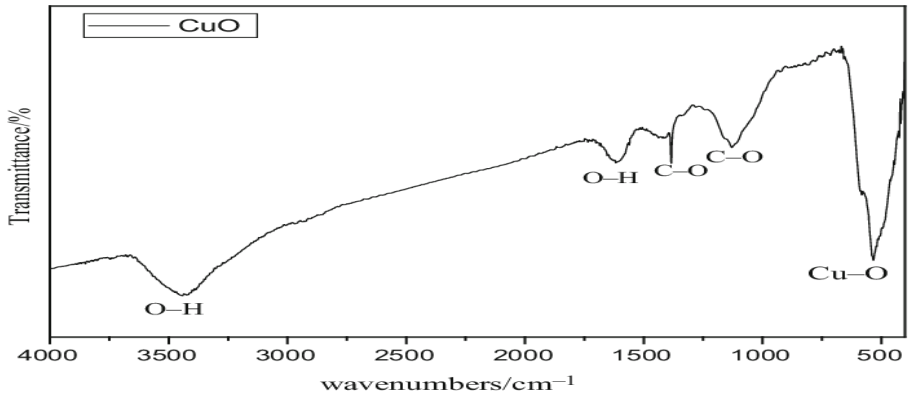
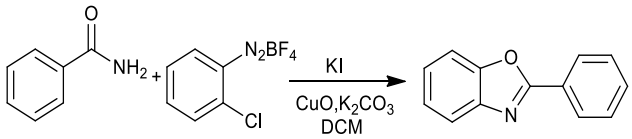


Figure 3: FTIR

3. **Application of MO**:
CuO prepared is further used as catalyst for coupling reaction in the formation of new C-N and C-O bonds. To illustrate this application following coupling reaction is taken where biologically important Benzoxazole is prepared using amide and aryl diazonium salt.



Conditions of temperature and solvents are optimised at 2 hours of heating and effects of equivalents of CuO is shown below

Sr.No	Equivalents of catalyst	Temperature (^oC)	Yield (%)
1	1	110	68
2	**2**	**110**	**85**
3	3	120	85
4	4	120	82

Reaction conditions: amide(1mmol), diazonium salt (1mmol), catalyst (1mol %), solvent (2 mL), KI (1.5mmol), K_2CO_3 (3mmol) 110^0C, time 2 Hrs; isolated yield

4. **Result and Conclusion**: Efficient, economical, base free protocol for benzoxazole synthesis has been developed with considerable good yield, high functional group tolerance, cost effective (due to use of diazonium salts). Moreover, Cuo NP used is prepared

by reverse micelle which is biocompatible. Therefore, it has prospectus to use in biological systems for diagnose metabolism and also for curative action in case of diseases and deficiencies.

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78

Synthesis, Charecterization and Biological Evaluation of Coumarin – Chalcone Derivatives

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ABSTRACT –
In the present study, an attempt has been made to synthesize and characterize some coumarin-chalcone derivatives and to evaluate them for their anti-microbial activity. The compounds were prepared as per the reported procedure in literature. The physicochemical characteristic like melting point, percentage yield, Rf value were evaluated. The synthesized compounds were characterized by IR, NMR and Mass spectroscopy. Compounds exhibited good antimicrobial activity when compared with standard. Further, there is a large scope for the development of other derivatives and their pharmacological screening. Since, the synthesized scheme is simple and now well established it would be easy to synthesize other derivatives by incorporating various substitutions and screenings them for other pharmacological activities like Antibacterial, antiviral, anti-tumor, anti-hyperglycemic, analgesic, anti-inflammatory, Moreover the newly synthesized Derivatives can be subjected for QSAR analysis and docking to emphasize the Pharmacophoric requirement and to study drug-receptor interaction and binding for specific target.

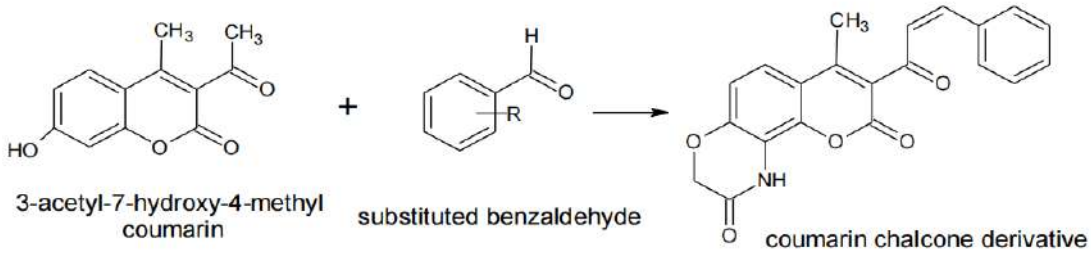
Keywords – Chalcone derivatives, Coumarin, Anti-microbial activity

INTRODUCTION –

Coumarin nucleus is widely distributed in nature in plant kingdom and forms an important class of oxygen heterocycle[1]. Over the years, coumarins have been established as well-known naturally occurring oxygen-heterocyclic compounds isolated from various plants[2]. They are the family of lactones containing benzopyrone skeletal framework that have enjoyed isolation from plant as well as total synthesis in the laboratory. The plant extracts containing coumarin-related heterocycles are employed as herbal remedies in traditional systems of medicine. The synthesis of coumarin derivatives has attracted considerable attention of organic and medicinal chemists due to its wide usage in food additives, fragrances, pharmaceuticals and agrochemicals. Given this, coumarins have attracted intense interest in recent years because of their diverse pharmacological properties. Hence, many researchers have reported different biological activities of coumarins derivatives such as antibacterial, antiviral, antitumor, anti-hyperglycemic, analgesic, anti-inflammatory activities and other pharmacological activities[3-11]. Chalcones are α,β -unsaturated ketones which constitute an important group of natural products that serve as precursors for the synthesis of various heterocyclic compounds like pyrimidines, imidazoles, pyrazoles, 2- pyrazoline and flavonoids[12,13]. Cyclization of chalcones, leading to thiazines, pyrimidines, pyrazoline has been a developing field within the realm of heterocyclic chemistry for the past several years because of their ready accessibility and the broad spectrum of biological activity of the products as antimicrobial, antibacterial, antifungal, antiprotozoal, anti-inflammatory substances[14]. With this background it has been thought worth to synthesize some novel heterocyclic compounds comprising of chalcone and coumarin in a single moiety. Also, to evaluate these new compounds for their potency as an anti-microbial agent.

MATERIAL AND METHOD

SYNTHESIS OF COUMARIN CHALCONE DERIVATIVES



A mixture of 3-acetyl-7- hydroxy-9H-benzopyrano- 1,4-oxaxin -2,9- dione and substituted aromatic aldehyde was stirred for 12 hr. under refluxed at temperature 60° C to obtain coumarin chalcone. The compounds were characterized by Infra-red, Mass and NMR Spectroscopy. *In-vitro* antimicrobial activities of synthesized compound were studied by pour plate method using ciprofloxacin as standard for antibacterial and ketoconazole as for antifungal activity respectively. The synthesized compounds were evaluated for their anti-bacterial activity against *Staphylococcus aureus* and *Escheria coli* and antifungal activity against *Aspergillus Niger*. The activity of synthesized compounds showed that synthesized compounds exhibited good antibacterial activity and antifungal activity.

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79

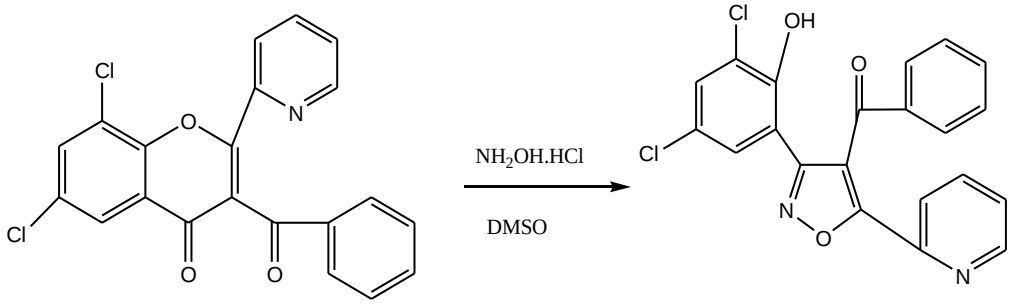
Synthesis and Characterization of (3-(3,5-dichloro-2-hydroxyphenyl)-5-(pyridin-2-yl) isoxazol -4-yl)(phenyl) methanone with microwave irradiation.

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Abstract:
Isoxazoles[1] is an unsaturated aromatic heterocyclic compound containing three carbon one oxygen and one nitrogen in a ring atom. Isoxazole being an azole with an oxygen atom next to the nitrogen exhibits a broad spectrum of biological activity and also forms a part of various biodynamic agents[2]. A mixture of 3-benzoyl-6,8-dichloro-2-(1-phenylprop-1-en-2-yl)-4*H*-chromen-4-one (VIa) (0.01 M), hydroxylamine hydrochloride irradiated with DMSO in microwave.

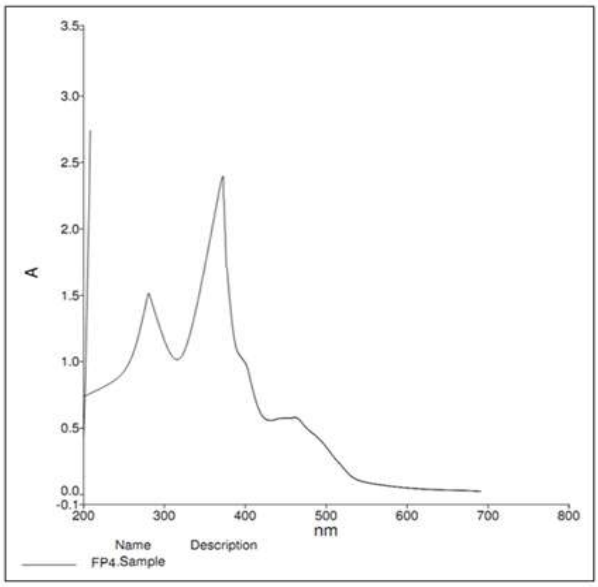
Introduction:
Isoxazole being an azole with an oxygen atom next to the nitrogen exhibits a broad spectrum of biological activity and also forms a part of various biodynamic agents. The substituted isoxazoles are also considered to be important structure due to their versatility toward chemical transformations to useful synthetic intermediates such as 1,3-dicarbonyl, 1,3-iminocarbonyl; and γ-amino alcohols.
The Chlorosubstituted isoxazoles have a wide range of pharmaceutical applications. In most of the skin creams substituted isoxazoles are the main constituents. Various kinds of skin diseases are cured by chlorosustituted isoxazoles. The healing process of skin specially done by the plant extract found in nature. It is interesting to notice that structure of isoxazole is found in plant extract used for healing process.

Methods of preparation:
A mixture of 3-benzoyl-6,8-dichloro-2-(pyridin-2-yl)-4*H*-chromen-4-one (VIc) (0.01 mol) and hydroxylamine hydrochloride was irradiated in DMSO (20ml) containing 0.5ml of piperidine for 3 min. 15 sec. in microwave. After cooling the mixture, it was decomposed into the ice and solid product thus obtained crystallized from methanol. The gray coloured crystals of the compound (IXc) were obtained. Yield: 70%, m.p: 191^{0}C.



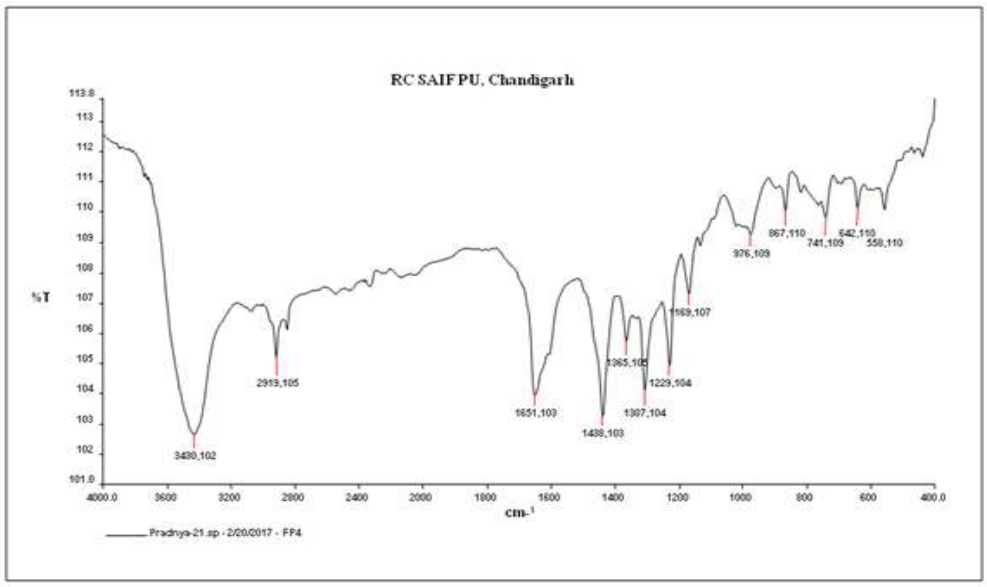
MW, 800 W, time: 3 min. 15 sec., Solvent: DMSO.
Microwave: 3 min. 15 sec, Yield: 70%
Conventional: 1 hour 20 min., Yield: 69%
All the synthesized compounds have been characterized on the basis of their chemical properties and spectral data.

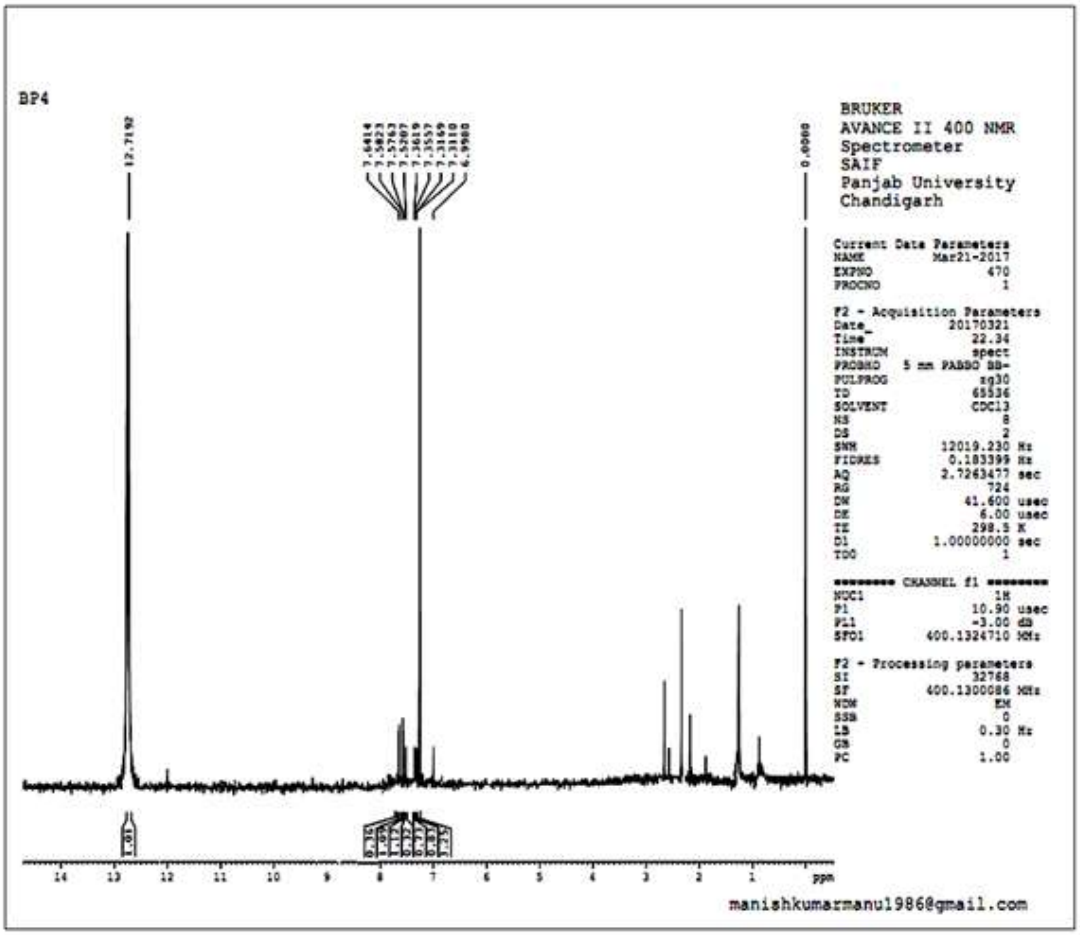
1. The UV-VIS spectrum of the compound **(3-(3,5-dichloro-2-hydroxyphenyl)-5-(pyridin-2-yl) isoxazol -4-yl)(phenyl)methanone** showed λmax value 355 nm respectively corresponding to n→ π * transition.



2. The IR spectrum (Spectrum No.54) of the compound (Xa) and compound (Xd) (Spectrum No.57) recorded in KBr showed following main absorption bands.

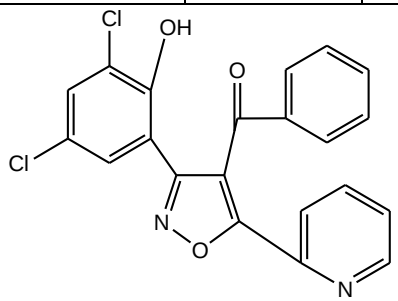
Compound IXd Spectrum No.51	Frequency (cm^{-1})	Intensity	Correlation
	3430	vb	Ar-OH stretch
	2919	vb	Ar C-H stretch
	1651	s	C=O stretch
	1438	s	C=N stretch
	1169	s	C-O stretch
	642	w	C-Cl stretch





1. The H^1 PMR spectrum of the compound (II) (Spectrum No.52) recorded in $CDCl_3$ with TMS as an internal standard. The observed chemical shifts can be correlated as:

Compound (IXd) Spectrum No.52	Chemical shifts δ ppm	Name of peak	No.of protons	Types of protons
	12.71	s	1H	Ar-O**H**
	6.99 to 7.64	m	9H	Ar-**H**



(3-(3,5-Dichloro-2-hydroxyphenyl)-5-(pyridin-2-yl)isoxazol-4-yl) (phenyl)methanone

Conclusion and Discussion of the Result

The short reaction time and expanded reaction range were offered by the microwave assisted synthesis. Chlorosubstituted isoxazoles need 6-9 min. exposure to microwaves incomparable to condensation reaction where it takes 2 hours so, it was thought interesting to save time in eco-friendly synthesis of chlorosubstituted isoxazoles.

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80

Microbial Examination of Nanoparticle of Tetra-O-acetyl-B-D-Glucosyl-5aryl-4-Dithiobiurets.

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Abstract :-
This discipline focuses on the design, characterization, manufacture, and use of structures, devices, and systems by manipulating form and size at the nanoscale scale. Recent years have seen an increase in the branch of current study known as nanotechnology. Here we screened for their antibacterial and antifungal activities against common pathogens like *Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Pseudomonas aeruginosa, Aspergillus niger* and *Penicillium.* Some compounds exhibit less to good activity while some are resistant to the said micro-organisms.

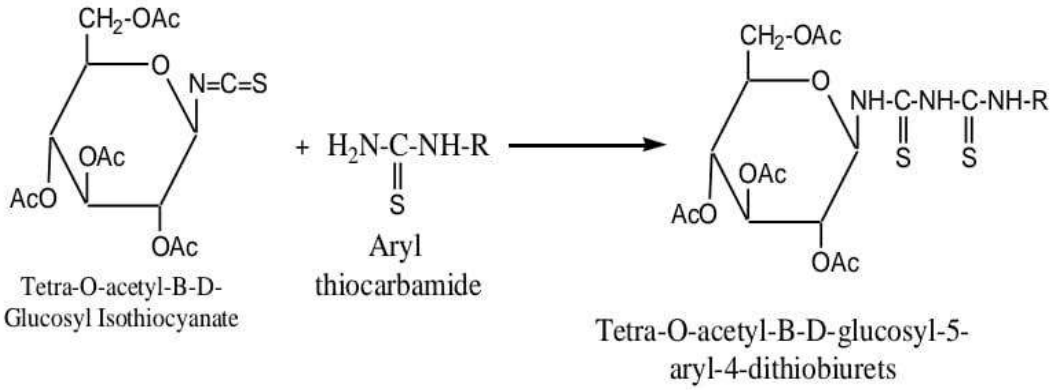
Keywords: TAG Isothiocyanate , Dithiobiurets , Nanoparticles and Antimicrobial Activities.
Introduction :- Carbohydrates are vastly diverse group of organic compounds occurring in all known plants, animal and microbial life. The function of carbohydrate is to provide energy and strength in plants and mammalian tissues they provide a whole variety of specialized functions ranging from cell and organ differentiation to immune protection for new born babies. Antimicrobial agents can be divided into many categories based on how they work and the objectives they serve. Depending on the category of microorganisms impacted, division may be made. Hence, substances that affect bacteria are known as bacteriostatic or bacteriocidal, whereas substances that affect fungus are known as fungistatic or fungicidal[1]. The cup plate agar diffusion method[2-3] provides a simple, convenient reliable test specially applicable in routine clinical bacteriology laboratory.
In particular, these substances have been effectively tested against a number of illnesses and have therefore earned medical significance. Chemical substances are used for treatment of diseases and has been known since the 1500's. The chemical substances used for the treatment of infectious diseases and diseases caused by the proliferation of malignant cell are called as chemotherapeutic agents. Antibacterial agents are any chemicals that prevent microorganisms from growing or that kill them. Despite the fact that many different compounds possess these qualities. The phrase is often limited to chemicals that are active at concentrations adequate for practical purposes when it is employed at sufficiently high concentrations.

Carbohydrate represents an important chemical class as many drugs and drug intermediates[4] are based on carbohydrates chemistry and many drugs such as amino glycoside antibiotics containing carbohydrate structure.

Among all carbohydrates our interest is to synthesized nitrogen linked glucosyl compounds due to its applications in medicinal chemistry and in many other ways[5-6]. Sugar isocyanate are versatile synthetic intermediate in carbohydrate chemistry. They have attracted considerable interest in synthetic and medicinal chemistry[7-8]. The glycosides have found use as divertic agent, analgesics, antidiabetic compounds and in many other ways[9]. Methyl β-lactosyl can significantly reduce the formation of tumor colonies in mice[10]. To increase its efficiency multivalent β-lactosyl have been synthesized in Roy's group. Heterocyclic derivative of sugars were found to possess anti-tumor and anti-bacterial activity. Besides these and other pharmaceutical applications of glycosyl urecides, they also found to possess applications in paper, textile and food industries

EXPERIMENTAL

The research work presented deals with the study of antimicrobial activities of newly synthesized N-glucosides against pathogenic organisms. Screening of following compounds were carried out against the microbes like *E. coli, P. vulgaris, S. aureus, P. aeruginosa, A. niger* and *Penicillium*.



Experiment No. 1:-1-Tetra-O-acetyl-β-D-glucosyl-5-phenyl-4-dithiobiuret. (IIIa)

To a toluene solution of tetra-O-acetyl- β -D-glucosyl isothiocyanate (0.005 M, 1.9g in 20 ml) was added toluene solution of phenyl thiocarbamide (0.005 M, 0.76 g in 10 ml) and reaction mixture was refluxed over boiling water bath for 3hr. Afterwards, solvent was distilled off and sticky mass obtained as residue was triturated several times with petroleum ether afford a white solid. It was crystallized with ethanol-water, m.p. 95°C. [Found: C, 50.30; H, 4.85; N, 7.93; S, 6.19, $C_{22}H_{26}O_9N_3S_2$. requires; C, 50.38, H, 4.96; N, 8.01, S, 6.10%].

The product was found soluble in ethanol, acetone, chloroform and benzene while insoluble in water and petroleum ether. It charred on heating with conc. sulphuric acid. It was found desulphurisable when boiled with alkaline plumbite solution. It was optically active and its specific rotation was found to be $[\alpha]D^{32}$ = -136.94° (c,0.74 in chloroform). The purity of the product was checked by TLC, Rf value 0.69 (CCl_4: EtOAc, 3:2)..

RESULTS AND DISCUSSION:-

The synthesis of N-glycosyl Dithiobiurets is a simple and reliable route. This strategy can be successfully applied to prepare a wide range of glycosyl Dithiobiurets and their derivatives which can be widely used for the preparation of biologically active molecules and good active lead in Medicinal Chemistry. Thus the synthesized novel N-glycosyl Dithiobiurets exhibits antibacterial and antifungal activities against the organisms tested. The method adopted in the synthesis and investigation is simple, efficient and inexpensive in synthesizing pharmacologically important molecule.

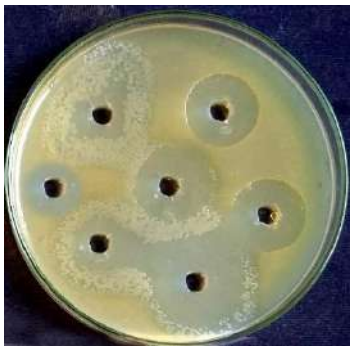
Antimicrobial Activity :- These newly synthesized thiocarbamides were screened for their microbial activity against different pathogenic microbes for their antibacterial and antifungal activities using well method16. The compounds were screened for antibacterial activity against *E. coli, P. vulgaris, S. aureus, P. aeruginosa, A. niger* and *Penicillium*. in potato dextrose agar medium. Procedure for antimicrobial screening Media used (Nutrient broth): Peptone – 10 g, NaCl – 10 g and yeast extract 5 g, Agar 20 g in 1000 ml of distilled water. Initially, the stock culture of bacteria were revived by inoculating in broth media and grown at 37 0C for 18 h. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 h old culture (100 µL, 104 cfu) and spread evenly on the plate. After 20 min. the wells were filled with different concentrations of samples. The control wells were

filled with Gentamycin. All the plates were incubated at 37 OC for 24 h and the diameter of inhibition zones were noted in mm. The activity was quantitatively assessed on the basis of inhibition zone

Table 1 : Antimicrobial activities of 1-Tetra-O-acetyl- β -D-glucosyl-5-aryl -4 dithiobiurets (I a-g)

Compounds	*E.coli*	*P.vulgaris*	*S.aureus*	*P.aeruginosa*	*A.niger*	*Penicillium*
I-a	+++	+++++	+++	++++	++++	++
I-b	+++	+++	+++	++++	++	+++
I-c	++	++	+++	++++	++	++++
I-d	++	++++	+++	++++	+++	+++
I-e	++	++++	++	++++	+++	++
I-f	--	+++	++++	++	+++	++++
I-g	+++	+++	+++	++++	+++	++

N.B. : ++++ Strongly active (above 20 mm)
+++ Moderately active (15 mm to 20 mm)
++ Weakly active (8 mm – 14 mm)
- - Inactive (below 8 mm)
Bore size = 7 mm





The compounds 1-tetra-*O*-acetyl– β -D-glucosyl-5-aryl-4-dithiobiurets (I-7) showed comparable activity. Compounds 1,2,3 showed strong activity against *P.vulgaris* and *S.aureus Penicillium*. Compounds 1-7 showed moderate activity against used microorganisms.

CONCLUSION

Derivatives were synthesized and characterized for their structure elucidation. Various chemical and spectral data supported the structures. Some of the compounds synthesized showed promising antimicrobial activities. The newly synthesized thiocarbamides and thiocarbamates exhibits comparable antibacterial and antifungal activities against the organisms tested. The method adopted in this investigation is simple, efficient and inexpensive and is useful in synthesizing pharmacologically important molecules. The method adopted in the synthesis and investigation is simple, efficient and inexpensive in synthesizing pharmacologically important molecules.

Acknowledgement

Authors are thankful to PDKV Akola for providing the spectral data and also to DR. V. D. Nanoty Principal, Shri R. L. T. College of Science, Akola for providing necessary facilities

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81

Synthesized PANI/Cu-NPs / Aloe-Vera thin films Biocomposites for ammine gas sensor stimulator.

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Abstract:
The synthesized polyaniline disperse Copper Nano particle (Cu-NPs) by the usage of ultrasonicator, microwave instrumentation approach to metal salt on Aloe Vera Leaf Extract thin film on glass subtract through chemically oxidative polymerization approach. The cupper chloride metallic salt disperse Nano particle (Cu-NPs) Stabilized on Aloe Vera Leaf Extract. The secondary phytochemical of Aleovera leaf plant extract polyphenols stabilizing and capping system for the more balance the cupper metallic chlorides. We synthesized PANI-Cu -NPs. Aloe Vera leaf extract studied their U.V., FTIR, XRD and Electronic Microscopy, Characterization for electrochemical behavior and current -voltage characteristics. The four -probe instrumentation system shows that the PANI-Cu-NPs modified electrode turned into accurate conductivity and stability on glass substrate. The thin film of PANI-Cu-NPs discovered gas sensing conduct for 10-50 ppm ammine gas sensor

Key word: Polyaniline, I-R Characterization, Thin film, PANI-Cu-NPs and Biocomposites

Introduction:
The biomaterial sciences include systematic study of engineering materials with various application purposes. A biomaterial is an engineering material which is specific range of properties like to evaluate the chemical, physical, mechanical and biological properties. Due to this synthetic polymer can be merged with biomaterial including metals, ceramics, composites and hybrid systems (1-2). The last three decay the numerous scientific efforts and publication reported related to biomaterial. The biomaterial science is a multidisciplinary area in science and technology included medicinal chemistry such as inert material gold, silver, and platinum, used in the early designed bone fracture plates like acrylic methyl methacrylate polymer or commercialized polymers such as Dacron used in the vascular implants and the heart valves (3-4).

Polyaniline exhibits excellent characteristic such as good electrical conductivity also environmental stability and an easy synthetic route. The synthetic biocompatible polymers show great physicochemical properties. The polymers PANI are the most commonly investigated IEPs because of several feature like good thermal stability, cost effectiveness of the used aniline less expensive monomer, simple synthetic procedure and good conductivity(5). PANI included metal salt materials have widespread application in the electronics, sensor, smart material batteries optical devices and biomaterial (6).
In this paper we reported the synthesis PANI-Cu-NPs -Aloe Vera hybrids thin film composites on glass substrate via simple chemical oxidative polymerization technique by using ultra sonicator. The Cu-NPs are first synthesized through the reduction of copper chlorides salts with Aloe -Vera leaf extracts of polyphenol. It is believed that these polyols can play a vital role as stabilizers/capping agents in the production of the Cu-NPs nanoparticles. The Novelty of this works is that plant extract polyols as well as flavonoids are used to stabilize the Copper particle in formation of thin films on glass substrate that is biomaterial or composites is synthesized and their utility for electrochemical characterizations in different application as sensor.

2. Materials and Methods

2.1 Materials and chemical

Aniline and Ammonium oxysulphides from Sd -Fine chemical are used. Aniline distilled prior to use. The copper (II) chloride hexahydrate ($CuCl_2.5H_2O$, >98%) was from Sd-Fine chemicals. Aloe-Vera was bought from a local college medicinal garden. Double Distilled deionized water (DDW) was from the analytical laboratory, Chemistry Department, was used for all aqueous preparations.

2.2 Extraction of Aloe-Vera gel and Cu -NPs synthesis

We are collected the fresh leaves of Aloe-Vera was bought from our college medicinal garden and remove the hard green coat from leaf by using knife, the after near about 10 g semi liquid parts gel and 10 ml of double distilled water are mixed in 100ml beaker by using ultra sonicator for 20 minutes. The resultant supernatant was collected, filtered and stored at 10 °C before use. The CuNPs were prepared by adding 0.1 M to 0.01M Copper chloride solution to the Aloe-Vera extract (supernatant at ambient temperature) in a series of 1:1,1:2,1:3,1:4,1:5 and also 5:1,4:1,3:1, 2:1 volume ratio. The mixture was hand shaken for 1 min and allowed to stand at room temperature for 30 minutes in ultra sonicator at 40 to 70 °C to prepare the nanoparticles. The all beaker kept in refrigerator for 24 hour at 10°C.

2.1 Synthesis of PANI-Cu NPs of Aloe-Vera films.

The optimize stoichiometric concentration of 2ml aniline and 0.05, upto 0.1 M Concentration of Cu-NPs of Aloe-Vera extract solution added to in series of 100 ml beaker with glass substrate to oxidized with 0.5 M ammonium peroxidisulphate under continuous stirring at room temperature in hydrochloric acid solution and kept in ultrasonicator for 20 minutes then cool it below -10 °C freezers for 24 hours to obtained homogenous stable thin film formation. The thin films substrates wash with deionized water kept to dry at room temperature with drier. The Figure shown in Fig 1.1 is that Synthesis of PANI-CuNPs of Aloe-Vera films after oxidation the formation Biocomposites films of PANI-CuNPs and Fig 1.2 indicates the formation of thin films of PANI--CuNPs on Glass substrate.



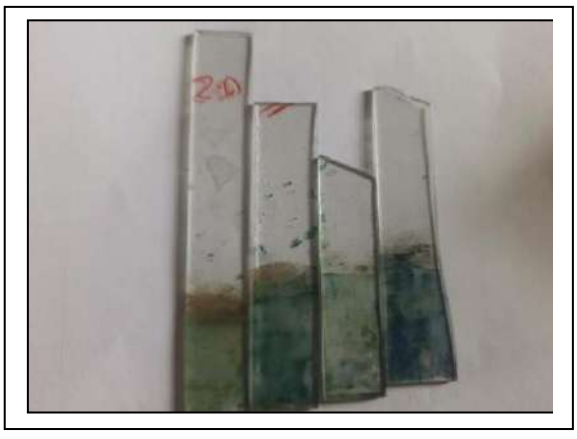


Fig 1.1 PANI-CuNPs of Aloe-Vera after oxidation Fig 1.2 thin films of PANI-CuNPs

2.2 Characterization Technique of the PANI-CuNPs

The Synthesized biocomposites of PANI-CuNPs dissolved in DMSO solvent to observe U.V.-Visible spectroscopy was recorded on UV- VIS Spectrophotometer Carry Agilent Tech at central instrumentation cell, Department of chemistry SGBAU, Amravati for formation of biocomposites and electronic transition is present to this biomaterial to show the electrochemical behaviors. The same composites solvent observed FTIR spectra were recorded on Bunker Alpha-T FT IR Spectrometer at central instrumentation cell, Department of chemistry SGBAU, Amravati for identification of functional group present and this functional group have vibration and rotation stretching of molecules. The XRD Spectra of dry powder observed by powder XRD spectroscopy for find the copper metal present in this biocomposites formation of biomaterials of Aleovera plants and metal dopant is this biocomposites. The application point if we need morphology of biocomposites is necessary this morphology observed by using High electron density microscopy by Department of Botany with in same institutes. The ectro-chemical behavior, Current –Voltage characteristics, and ammine gas sensing behavior were observed by four probe technique in Department of Physics BAMU university.

3. Results and Discussion.

3.1 Electron microscopy of PANI-CuNPs film.

To the view of application, we observed the morphology and structure of film for gas sensing application as well as I-V chaterization and other advance application like electronic device like ploy membrane, biomaterial, battery electrode or capacitor we need the uniform formation of films having their particular appearance of like tubular, granular or some Nano size metal slat occurrence of film observed.

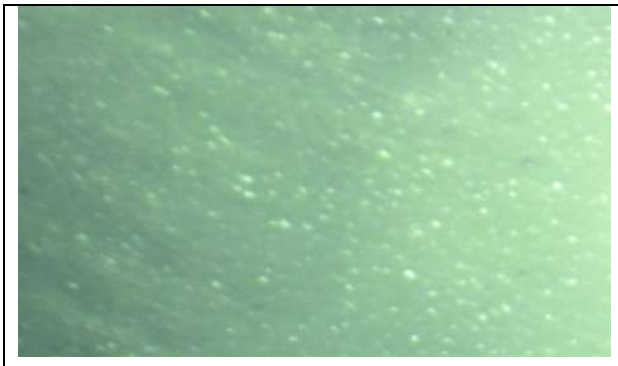


Fig 3.1**Electron microscopy of PANI**

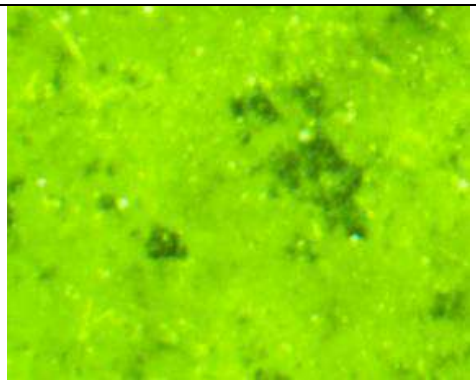


Fig 3.2**Electron microscopy of PANI-CuNPs**

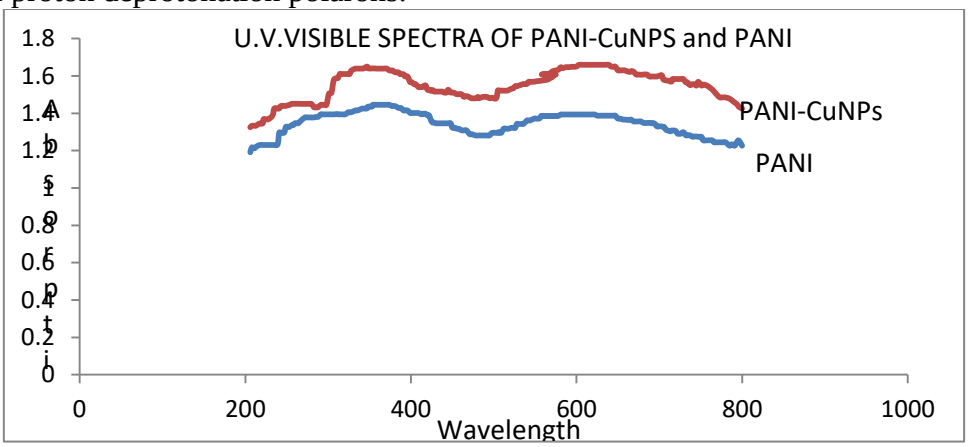
In Fig 3.1 observed that the Electron microscopy image of polyaniline films on glass substrate is uniform, having porous in morphology which applicable in chemical gas sensing as well as electrochemically behavior nature can be applicable for battery storage application as well as chemical and biological sensor. In Fig 3.2 observed that the Electron microscopy image of PANI-CuNPs Biocomposites of Aleovera plant which is uniform, porous dark green in colouration, the film having some dark globular spot confirm the presence of cupper metal in granule morphology which have active role in gas sensor application. These two images confirm that there is formation PANI-CuNPs Biocomposites.

3.2 U.V Spectra of PANI-CuNPs film.

The U.V.-Visible spectroscopy was studied in range between 200nm to 700nm after dissolution of PANI and PANI/Cu-NPs / Aloe-Vera thin films in DMSO solvents. The spectrum shows a prominent peak at absorption maxima of 330 nm which has been assigned to the $\pi \rightarrow \pi^*$

transitions of the Aloe-Vera polyols. A broad peak extending from 310-390 nm with absorption maxima at 330 nm was seen.

The new peak formed was slightly shifted bathochromically compared to the 282 nm peak of the Aloe-Vera extracts. This peak at 282 nm and the smaller hub at around 330 nm have been shown to be due to the presence of the Cu-NPs nanoparticles in the Cu (II) state. It means the reductant polyols within the matrices successfully reduced the Cu (II) ions to indicating the formation of the Cu-NPs polyols hybrid. The PANI/ Cu-NPs / Aloe-Vera films composite films have conducting in nature it observed band at 560 nm to 690nm due to presence of conducting polaron of protonated ring of polyaniline. The PAni-Cu-NPs show in U.V. spectra it more intensive peak or activated to n→π* at 684 nm to delocalization of lone pair of electron with Cu-metal proton deprotonation polarons.



In Fig 3.2 U.V Visible spectra of PANI-CuNPs

3.3 FTIR Spectra of PANI-CuNPs film.

FT-IR spectra of PANI-CuNPs exhibited the characteristic absorption bands of emeraldine salt at 1518 and 1616 cm^{-1}, which correspond to the C- C stretching vibration of benzenoid (N -B-N) and quinonoid (N =Q= N) ring, respectively [7]. The peaks in the range of 1300–1400 cm^{-1} as arise from C-N stretching vibrations of the secondary aromatic amines, while the intense absorption peak at 1193 cm^{-1} is associated to the B- NH -B and protonated Q =NH^{+}-B stretching modes of PANI chains [8].

Figure 3.3 of the hybrid PANI/Cu-NPs/Aloe-Vera bio composite materials indicated a considerable red shift (∼15–20 cm^{-1}) of the N-B-N and N =Q=N vibrational bands at ∼1501 and ∼1600 cm^{-1}respectively, suggesting interaction of PANI chains with anionic heteropolyacids. The IR spectra of the hybrid samples indicate the presence of Cu-Od (terminal bonds) and Cu-Ob -Cu (bridge bonds between the corner-sharing CuCl octahedra; M = Cu) stretchingvibrations at ∼972–988 and ∼879–890 cm^{-1} respectively [9]. The intense absorption bands at∼1140 and ∼1080 cm^{-1} observed in the samples of Cu-Nps –Aleovera and PANI–Cu-Nps -Aleovera are ascribed to the clusters, respectively. The aromatic C-N and O-H stretching occurs at 3550cm-1 presence of aromatic Ar-OH and Ar-NH that alkolides and amino nature of fictional groups. The C-O, C-N Stretching at 1774cm^{-1} and 1914cm^{-1}. The various secondary metabolites all confirm by the presence of their functionality stretching and bending occurs in this FTIR spectra of PANI–Cu-Nps.

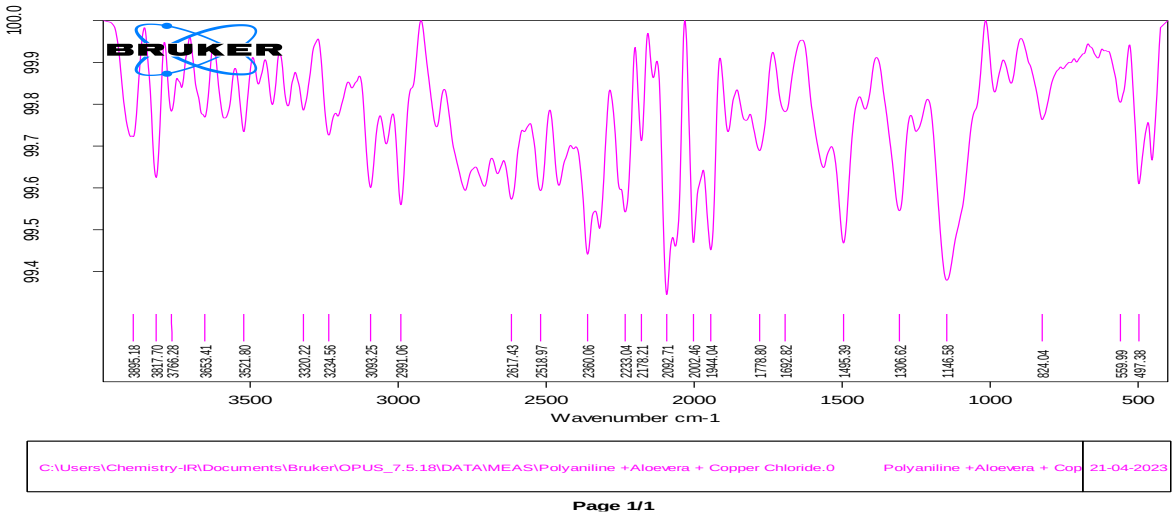
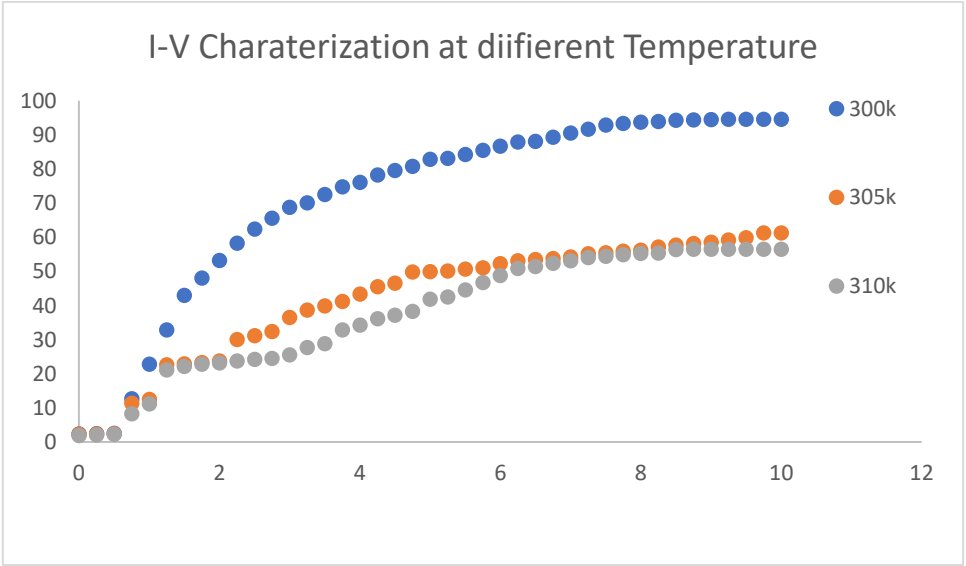


Figure 3.3 of the PANI/Cu-NPs / Aloe-Vera bio composite

3.4.I -V characterization of PANI-CuNPs film.

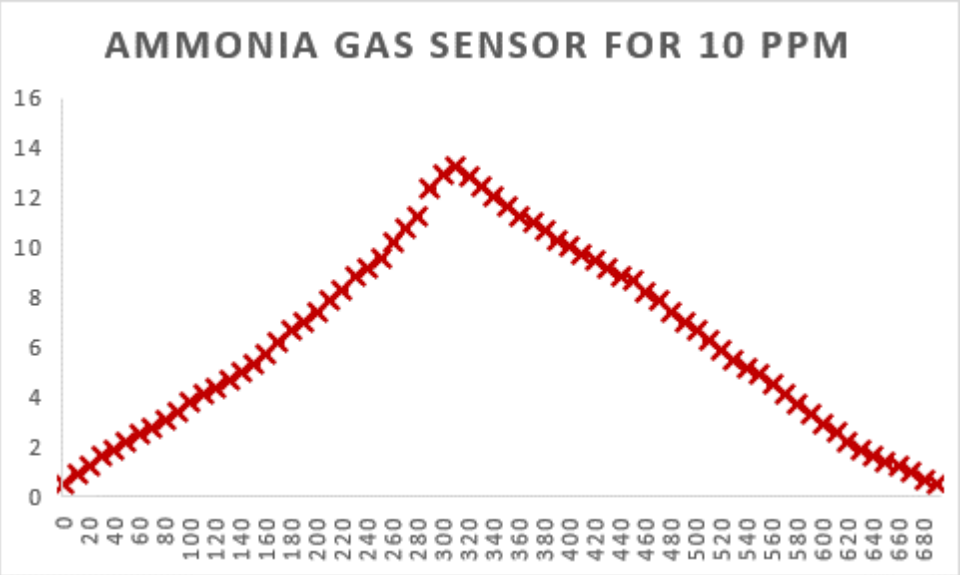
The I-V characterization measurement of the PANI /Cu-NPs /Aloe-Vera films was recorded by an indigenously developed computer controlled using four- probe method at room temperature. The current–voltage (I-V) characteristics of the synthesized PANI /Cu-NPs thin film was studied to ensure a ohmic or non ohmic behavior of the film. A linear and non lenar relationship of the I-V characteristics shown in Fig.3.4. reveals that the PANI /Cu-NPs composites film has at 300k ,305 k and 310k of different temperature for applied the voltage at 0.5 to 10 voltages applied then for 300k it observed that initial from 0.5 ev potential to 3.5 it shown liner ohmic charter but to increase in voltage from 3.5 to 7ev voltage it shown bent or deflected in nature a then from 7 ev it stabilized and steady in nature appearance. The same film at 305k near about same behavior but 310k it disappears the linearity its non linear in nature. The average conductivity at 300k to applied the potential it shown in between $2.6x10^{-5}$s/cm to $70.6x10^{-5}$s/cm.



3.5. Ammine gas for 10 -50ppm sensitivity PANI-CuNPs film.

The synthesized having good morphology film of PANI-CuNPs film observed ammine gas sensing conduction for low 10 ppm to change 50ppm hinger level. the films expose to 10 minutes for passing the ammine gas and observe the change in resistivity recorded by using computer control four probe system and to observer the recovery period the again expose to higher 50ppm ppm level. Due to present of Cu NPs biomaterial, it has recover and response are good because the film have conducive as well as uniform and porous in condition it

applicable to gas sensing behavior it can again expose to Carbon monoxide gas but it dangerous to handle at our laboratory to take care safety purpose. Fig 3.5 observed that the ammonia gas exopse for 10ppm level. 10 ppm ammonia gas exposed to gas sensor chamber for 5 minute (300 second) and observed the change in resistivity of film, which is continuously increasing but the for recovery of this gas the chamber is open and observered the change bin resistivity it required 6.5 minutes (690 second) the recovery time is more as compared to response time by using four prob method.



Conclusion:

This paper deal with study of PANI /Cu-NPs / films biomaterial composite. The characterization techniques such as U.V, FTIR and EM analysis confirmed that Copper chloride metal salt with Aleo Vera were successfully dispersed into the PANI matrix. Effect of different concentration of cupper with Aleo vera on structural, electrical and properties of PANI /Cu-NPs Biocomposites were studied. FTIR analysis showed good intermolecular interaction between PANI Cu-NPs / Aloe-Vera matrix. The surface morphology of PANI /Cu-NPs examined using EM analysis which is applicable for 10 ppm ammonia gas sensing behavior. The I-V Chaterization at highest conductivity with a value of $2.6x10^{-5}Scm^{-1}$, observed electrochemical behavior which is linear and nonlinear behavior.

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82

Structural and Ion-Exchange Properties of Copolymer Derived from 4, 4'-Biphenol - Benzidine - Formaldehyde

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Abstract

A new copolymer resin has been synthesized by condensation polymerization reaction of 4,4'-Biphenol and Benzidine with Formaldehyde in presence of 2M hydrochloric acid as catalyst. Composition of resin was determined on the basis of their elemental analysis and further characterized by UV-Visible, Infra-red and Nuclear magnetic resonance spectroscopy to confine the most probable structure of synthesized copolymer.

Newly synthesized copolymer was proved to be a selective chelating ion-exchanger for certain metal ions and were studied for Fe^{3+}, Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} and Pb^{2+} ions using their metal nitrate solutions. A batch equilibrium method was employed to study the selectivity of metal ions uptake involving the measurements of the distribution of a given metal ion between the copolymer sample and a solution containing the metal ion. The study was carried out over a wide pH range, shaking time and in media of different electrolytes at different ionic strengths. Distribution ratios of metal ions were found to be increased by rising pH of the solutions. Hence, it can be used to recover certain metal ions from waste water, for the purpose of purification of water and removal of iron from boiler water.

Key words Copolymers, Ion-exchangers, Distribution ratio, Metal ion uptake, Distribution ratio.

1. Introduction

Ion exchangers are often employed in chromatographic separation of cation mixture by using complexing agents to increase the efficiency of separation. Process of ion exchange between liquid and solid phase in which the complex equilibria are involved, includes conventional cation exchanger resin containing sulphonate or carboxylate group, is used which do not form the complexes with the cations present and the complexing agent is present as a solute in liquid phase. Chelating resins having a functional group as a complexing agent fixed to the matrix is used when either the liquid phase may or may not contain a complexing agent as a solute, permits the solution of some difficult analytical problems like separation of similar ions and the enrichment of trace elements in a simpler and far less tedious manner than the methods applied so far. This challenge has encouraged the numerous attempts by analytical chemists for synthesizing new chelating ion exchanger with definite selectivity towards certain ions or group of ions.

The introduction of ion exchange terpolymer resins offered new possibilities for the separation of species, and the application of various complexing agents has lead to much extremely effective separation procedure. In an analytical as well as synthetic inorganic chemistry, there exist a need for good chelating polymers that combines the ease of operation of conventional ion exchangers and selectivity of organic analytical reagents. The selectivity of most of the reagents for metals remains predominantly in their ability to form the complexes

with certain cations. Attempts have been made in the early fifties of the twentieth century to synthesize organic polymers which contain complex forming groups as exchanging functions. The selective behavior of these resins is based on the different stabilities of the metal complexes on the resin at appropriate pH values. The optimum conditions for maximum efficiency for given separation can be established by variation of the pH with time interval.

Selective removal, separation and recovery of metals from industrial effluents is a problem of environmental and economic concern, in consideration of the more stringent limits enforced for pollutants control and raising costs of raw materials. Ion exchange as a conservative technology allows for selective removal and recovery of heavy metals. Chelating ion exchangers are suitable for this purpose in presence of one or more donor atoms as Lewis bases which are able to coordinate most of the toxic polyvalent metal ions acting as Lewis acids. Accordingly, the selectivity scale of different chelating exchangers toward metals reflects the stability of the corresponding metal-ligand complexes in the liquid phase.

Toxic and heavy metal ions, traces of organic and inorganic contaminants, radioactive nuclides are widely occurred in aquatic systems as a result of rapid globalization and industrialization. Sorption processes such as electrodeposition, coprecipitation, solid liquid extraction, activated charcoal etc. have been used for the removal of these contaminants. In recent years, terpolymer ion-exchange resins have been developed due to their wide application in waste water treatment and pollution control, hydrometallurgy, antibiotic purification and separation of radioisotopes, identification of specific metal ion and metal recovery [1-4]. A batch equilibrium method has gained a rapid attention of researchers because of its acute degree of selectivity, variety of sorbent phases and enhanced hydrophilicity [5]. Some publications on the synthesis, characterization and applications of chelating ion exchange resins from other researchers [6-18] and from our research group on some terpolymer resins have been reported [19-23].

Lutfor et al [6] have prepared a chelating ion-exchange resin containing amidoxime functional group, was characterized by FT-IR spectra, TG and DSC analysis and the chelating behavior was studied with Cu^{2+}, Zn^{2+}, Ni^{2+}, Cd^{2+} and Pb^{2+} metal ions. Removal of transition metals from dilute aqueous solution by carboxylic acid group containing absorbent polymers has been studied by Liu Z S and Rempel G L [12].

Extensive literature is available to interpret the experimental results in the light of practical applicability of various terpolymer resins. Ion exchange properties of terpolymer resins derived from *o*-nitrophenol and thiourea with paraformaldehyde by A. Burkanudeen et al [7]; and salicylic acid, melamine and formaldehyde by Gurnule et al [8] have been studied. The terpolymer derived from 2,4-dichlorophenyl acrylate/8-quinolinyl methacrylate and acrylic terpolymer derived from 8-quinolinyl methacrylate were found to be a good cation exchanger as it has pendant ester-bound quinolinyl group [9, 10]. Terpolymers derived from salicylic acid and formaldehyde with resorcinol [11], 2,4-dihydroxybenzoic acid-urea-formaldehyde [13], salicylic acid-biuret–formaldehyde [14], 8-hydroxyquinoline, guanidine and formaldehyde [15], anthranilic acid-resorcinol-formaldehyde [16], 4-hydroxyacetophenone -biuret-formaldehyde [17] have been proved to be good ion exchangers. A detailed study on preparation and characterization of a new class of polymeric ligand exchangers for selective removal of trace contaminants from water has been reported by Henry and coworkers [18].

For chelating resin, however, reported in the publications with respect to the desired requirement is seldom presented. But only occasionally, it proved to be valuable for separation on laboratory scale. In this context, as reported earlier [19-23], the present study has been carried out on synthesis, characterization, selectivity and ion exchange capacity of copolymer resin (4,4'-BP-BD-F) derived from 4,4'-Biphenol (4,4'-BP) and Benzidine (BD) with Formaldehyde (F).

2. Experimental

2.1 Materials

The chemicals, 4,4'-biphenol and benzidine from Acros Chemicals, Belgium and formaldehyde (37%) from S. D. Fine Chemicals, India of analytical grade purity were purchased. All the solvents like N, N-dimethylformamide, dimethyl sulphoxide, tetrahydrofuran, acetone, diethyl ether were used after double distillation. All the metal nitrates, indicators, electrolytes and disodium salt of ethylenediaminetetraacetic acid of analytical grade purity were used, procured from Merck, India.

2.2 Synthesis of 4,4'-biphenol-benzidine-formaldehyde (4,4'-BP-BD-F) copolymer resin

A new copolymer was prepared by condensation polymerization reaction as shown in Figure 1, by using the molar proportion 3:2:8 of reacting monomers i.e. 4,4'-biphenol (5.58 gm, 0.3 mol) and Benzidine (4.00 gm, 0.2 mol) with formaldehyde (30 ml, 0.8 mol) in presence of 2M HCl as a catalyst at temperature 130 ^{o}C in an oil bath for about 3 h of continuous heating with occasional shaking. Dark reddish brown colored solid product was immediately removed, filtered and purified by dissolving in 1:1 (v/v) conc. NaOH/water with constant stirring and then filtered. The resulting polymer sample was washed several times with boiling water and dried in a desiccator at room temperature. Further dried polymeric sample extracted with diethyl ether to remove the excess 4,4'-biphenol-formaldehyde copolymer which might be present along with the 4,4'-BP-BD-F copolymer. Finally, the terpolymer was passed through 300-mesh size sieves and kept in a vacuum over silica gel.

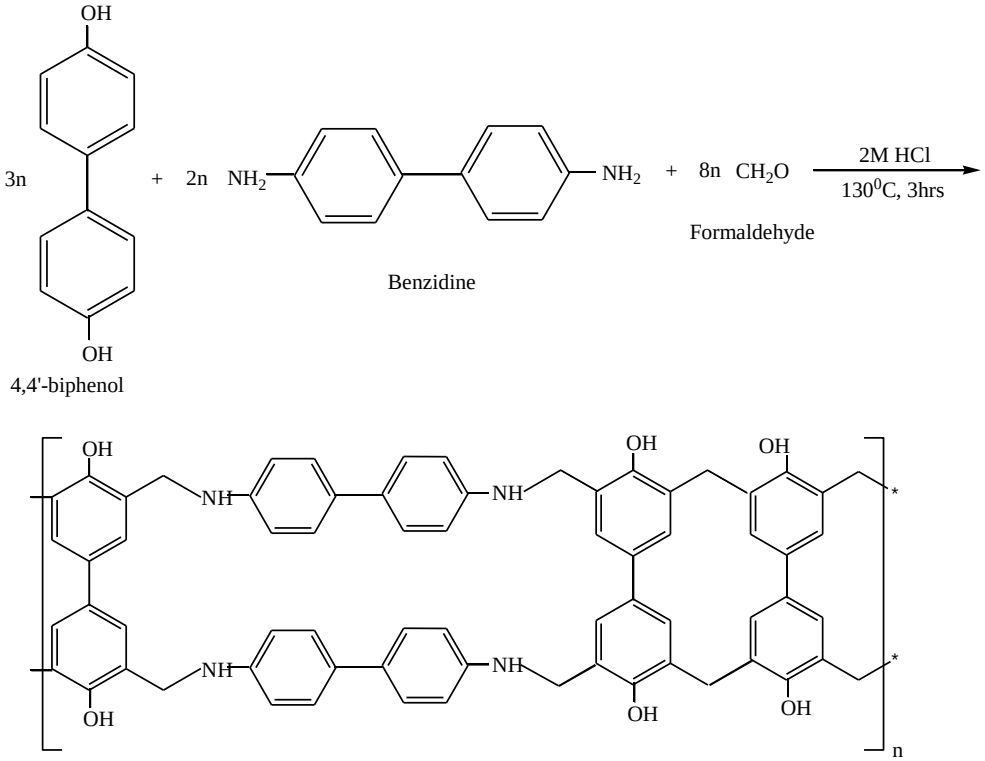


Fig. 1. Chemical reaction of 4,4'-BP-BD-F copolymer.

2.3 Characterization of copolymer by spectral studies

Terpolymer was subjected to elemental analysis for carbon, hydrogen and nitrogen on Perkin Elmer 2400 Elemental Analyser. UV-Visible spectra were recorded by preparing solution in dimethylsulphoxide on Shimadzu, UV-Visible double beam spectrophotometer in the range of 200-850 nm. Infrared spectra was recorded using KBr pellet in nujol mull on Perkin-Elmer-spectrum RX-I spectrophotometer in the range of 4000-500 cm^{-1}. ^{1}H-NMR studies were performed in solvent, dimethylsulphoxide, on Bruker Advance-II 400 MHz proton

NMR spectrophotometer. All the analytical and spectral studies were carried out at Sophisticated Analytical Instrumentation Facility (SAIF) Punjab University, Chandigarh.

2.4 Study of ion-exchange properties

As the batch equilibrium method has gained a rapid attention of researchers because of its acute degree of selectivity, variety of sorbent phases and enhanced hydrophilicity [5, 19-23] and hence has been applied to study the ion-exchange properties in the present investigation.

2.4.1. Determination of metal ions uptake in presence of electrolyte at different concentrations

The copolymer sample (25 mg) was suspended in an electrolyte solution (25 ml) of known concentration and the pH of the suspension was adjusted to required value by using either 0.1 M HNO_3 or/and 0.1 M NaOH, and was stirred for 24 h at 30 ^oC. To this suspension 2 ml of 0.1M solution of the metal ion was added and adjusted to required pH value, and then again stirred at temperature 30 ^oC for 24 h and filtered. The filtrate and washing of the solid product were combined together for the determination of metal ion content by titration against standardized ethylenediaminetetraacetic acid solution. The amount of metal ion taken up by copolymer was calculated from the difference between a blank reading and experimental reading. The experiment was repeated in the presence of several electrolytes at various ionic strength.

2.4.2 Evaluation of rate of metal ions uptake

Series of experiments, of the type described above, were carried out in order to estimate the time required to reach the state of equilibrium under the given experimental conditions, in which the metal ion taken up by the chelating resins was estimated from time to time, at temperature 30 ^oC, in presence of 25 ml of 1 M $NaNO_3$ solution. It was assumed that, under the given conditions, the state of equilibrium was established within 24 h. The rate of metal ions uptake is expressed as percentage of the amount of metal ions taken up after a certain time related to that at the state of equilibrium, using following relationship.

$$Metal\ ion\ uptake = \frac{Amount\ of\ metal\ ion\ absorbed}{Amount\ of\ metal\ ion\ at\ equilibrium} \times 100$$

2.4.3 Distribution of metal ions at different pH

The distribution of each one of the eight metal ions i.e. Fe^{3+}, Cu^{2+}, Hg^{+2}, Ni^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+} between the polymer phase and the aqueous phase was determined at temperature 30 ^oC in presence of 1 M $NaNO_3$ solution. The experiments were carried out as described above at different pH values and the distribution ratio (D), as defined, was calculated using following relationship.

$$D = \frac{Weight\,(mg)\,of\ metal\ \ ion\ \ taken\ up\ by\ 1\,gm\,of\ terpolymer}{Weight\,(mg)\,of\ metal\ ions\ \ present\ in\ 1ml\,of\ solution}$$

3. Results and discussion

The resin sample was dark reddish brown in color and the solubility was tested in commonly used solvents and found to be soluble in DMF, DMSO, THF and pyridine without any precipitation and degradation. It was characterized by elemental and various spectral analyses and further studied their ion exchange behavior.

3.1. Characterization of terpolymer resin

3.1.1. Elemental analysis

Elemental analysis was carried out for Carbon, Hydrogen and Nitrogen contents which agrees well with theoretically calculated values, as compared in Table 1 and derived its empirical formula ($C_{68}H_{54}N_4O$) and empirical formula weight (1054).

Table 1. Elemental analysis data of terpolymer.

Terpolymer	Monomer empirical formula	Empirical formula weight	Elemental Analysis (%)					
			C		H		N	
			Cal.	Exp.	Cal.	Exp.	Cal.	Exp.
4,4'-BP-BD-F	$C_{68}H_{54}N_4O_6$	1022	77.41	76.62	5.12	5.02	5.31	5.24

3.1.2. UV-Visible spectra

Pure DMSO solvent was used to record the UV-visible spectrum of terpolymer sample in the wavelength region 200-850 nm and shown in Figure 2. The spectrum displayed two absorption maxima in the region 255 and 298 nm. The former and more intense band may be due to n→π* transitions [24, 25] observed at 255 nm, indicates the presence of oxybiphenyl moiety. Hypsochromic shift observed in biphenyl may be due to introduction of -O- group between two phenyl groups which destroys the conjugation. Later and less intense band observed at 298 nm is accounted for π →π* transition which may be due to biphenol group.

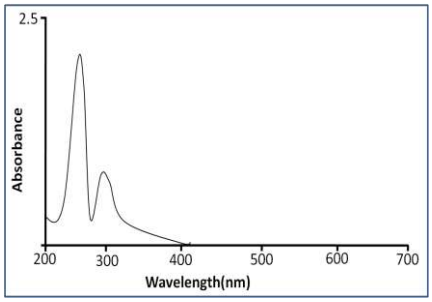


Fig. 2. UV-Visible spectrum of terpolymer.

3.1.3. FT-IR spectra

The FT-IR spectrum of terpolymer is represented in Figure 3 which shows a broad band, appeared at 3400.8 cm^{-1}, may be assigned to stretching vibration of the phenolic -OH groups, exhibiting intermolecular hydrogen bonding [26, 27]. Presence of weak peak at 2925.5 cm^{-1} describes the -NH- stretch in benzidine moiety which is present in terpolymeric chain [27]. Sharp and weak peak obtained at 2856.1 cm^{-1} indicates the presence of stretching vibrations of methylene -CH_2- group in the terpolymer chain [26]. Stretching vibration of >C=C< in aromatics is represented by a medium band displayed at 1662.8 cm^{-1}. C-O stretching in phenol is represented at 1250.5 cm^{-1}. Bending, wagging and rocking vibrations can be accounted by the presence of bands appeared at 1460 cm^{-1},1345-1350 cm^{-1}, 750-770 cm^{-1} respectively, may be due to presence of methylene bridges (-CH_2-) in the polymeric chain [28, 29]. The weak band appearing at 1010.5 and 837.7 cm^{-1} indicates the presence of tetrasubstitution in aromatic ring [27].

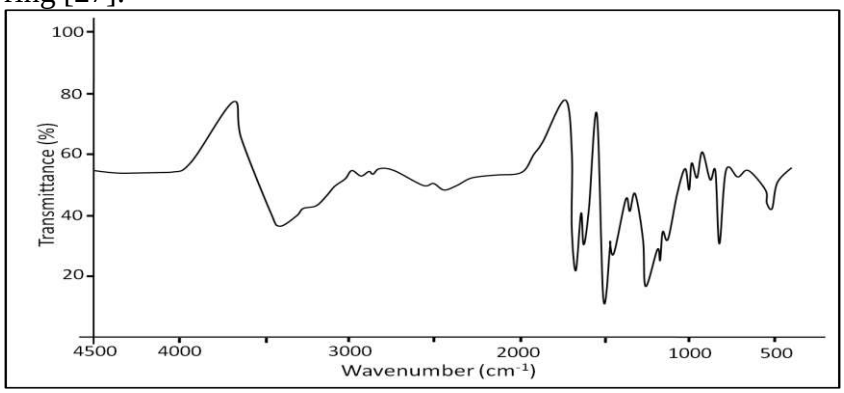


Fig. 3. FT-IR spectrum of terpolymer

3.1.4. *^{1}H- NMR spectra*

Solvent DMSO-d_6 was used to record ^{1}H-NMR spectrum and is represented in Figure 4; which reveals different pattern of peaks, since each of it possesses set of proton having different proton environment.

A significant downfield in chemical shift of proton of phenolic -OH group, observed at δ 7.9 ppm is due to intermediate proton exchange reaction of phenolic -OH group [28]. Weak singlet is observed at δ 7.4 ppm is due to aromatic protons. Doublet signal observed at δ 6.8 ppm may be attributed to methylene protons of Ar-CH_2-NH- moiety. In 4,4'-oxydianiline moiety, the doublet observed in the region δ 7.2 and δ 7.3 ppm is attributed to protons ortho to –NH and protons ortho to -O- respectively. A broad singlet observed at δ 6.7 ppm may be assigned to amino proton of -Ar-NH-CH_2 moiety and methylenic protons of Ar-CH_2-Ar moiety may be recognized as signal appearing at δ 3.4 ppm [27, 28].

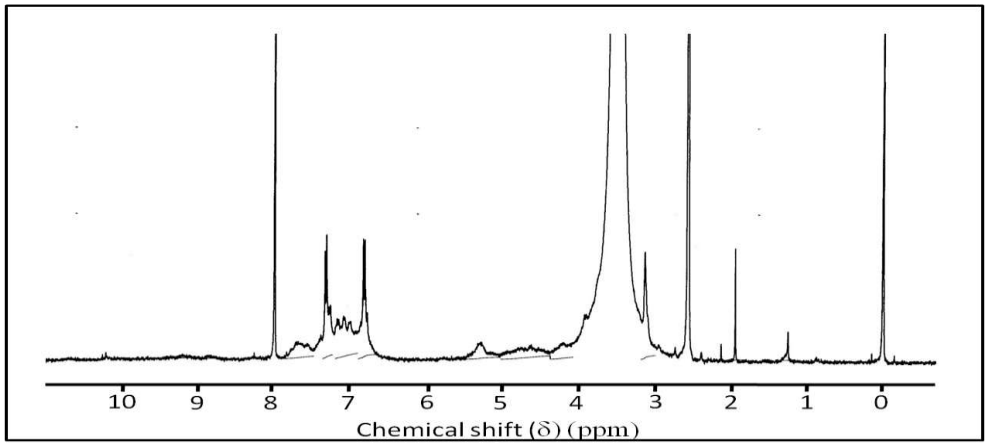


Figure 4. ^{1}H-NMR spectrum of terpolymer

On the basis of the nature and reactive position of the monomers, elemental analysis, UV-visible [24, 25], FT-IR [26, 27] and ^{1}H-NMR [27, 28] spectra, the most probable structure has been proposed as shown in Figure 1.

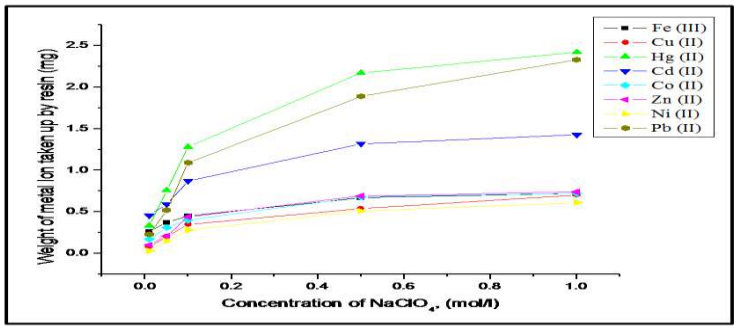
3.2 Study of ion exchange properties

To suggest the utility of newly synthesized terpolymer resins as ion exchanger for various applications, the study of influence of various electrolytes on the selectivity of metal ions, the rate of metal ion uptake and the distribution ratio of metal ions between the terpolymer and solution containing the metal ions, have been carried out. In a view to ascertain the selectivity of terpolymer resin, as ion exchanger, studies for the selected metal ions using batch equilibrium technique developed by Gregor et al and De Geiso [31] et al, have been carried out.

The results of batch equilibrium study are presented in Figures 5 to 10 in which aqueous solution of metal nitrate of Fe^{3+}, Cu^{2+}, Hg^{+2}, Ni^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+}; and electrolytes $NaNO_3$, NaCl, $NaClO_4$ and Na_2SO_4 were used. The ion exchange study was carried out using three experimental variables namely; a) Electrolytes at different ionic strength b) Shaking time and c) pH of the aqueous medium by keeping the two parameters constant. Only one parameter was varied at a time to evaluate its effect on metal ion uptake capacity of the copolymer [30, 31].

3.2.1 Effect of Electrolytes and their concentrations on metal ions uptake capacity.

The influence of ClO_4^-, NO_3^-, Cl^- and SO_4^{2-} at various concentrations on the equilibrium of metal-resin interaction has been studied and the results are expressed graphically shown in Figures 5 to 8. It shows that the amount of metal ions taken up by a given amount of copolymer depends on the nature and concentration of electrolyte present in solution. In presence of ClO_4^-, Cl^- and NO_3^- ions, the uptake of Fe^{+3}, Cu^{+2}, Hg^{+2}, Zn^{+2}, Cd^{+2}, Co^{+2}, Ni^{+2} and



Pb^{+2} ions increases with rise in concentration of the electrolytes. Further, it was observed that in presence of SO_4^{-2} ions, the amount of above metal ions taken up by the copolymers decreases with increasing concentration of electrolytes.

Moreover, higher increase in uptake of Fe^{+3}, Hg^{+2} and Pb^{+2} ions with increasing concentration of ClO_4^-, Cl^- and NO_3^- ions has been observed as compared to Cu^{+2}, Zn^{+2}, Cd^{+2}, Co^{+2} and Ni^{+2} ions, but it decreases in presence of SO_4^{-2} ions. It was considered that the anions like ClO_4^-, Cl^- and NO_3^- form weak association with the above metal ions while SO_4^{-2} ions may form stronger complexes. Thus, this association may affect the equilibrium which may be explained on the basis of stability constants of complexes with these metal ions and the results agrees well as reported earlier [19, 20].

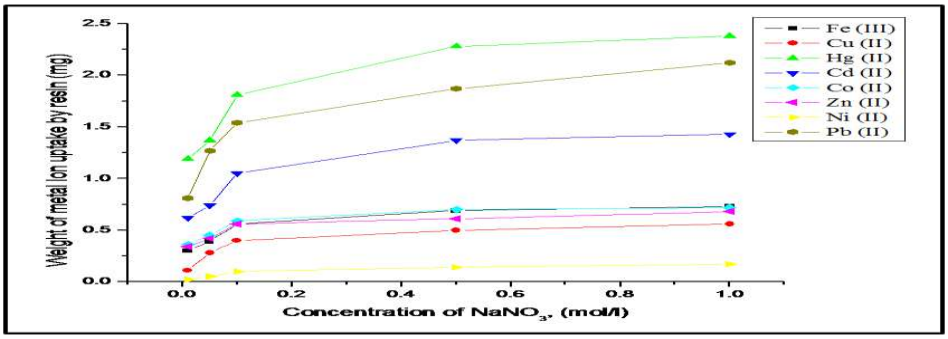


Fig. 5. Evaluation of the influence of different electrolytes on uptake of several metal ions[a] by terpolymer resin at different concentrations of $NaNO_3$ electrolyte solution.
[a][$M(NO_3)_2$]=0.1 mol/l; volume of metal ion solution = 2 ml; volume of electrolyte solution = 25 ml; weight of resin = 25 mg; time = 24 h; at room temperature

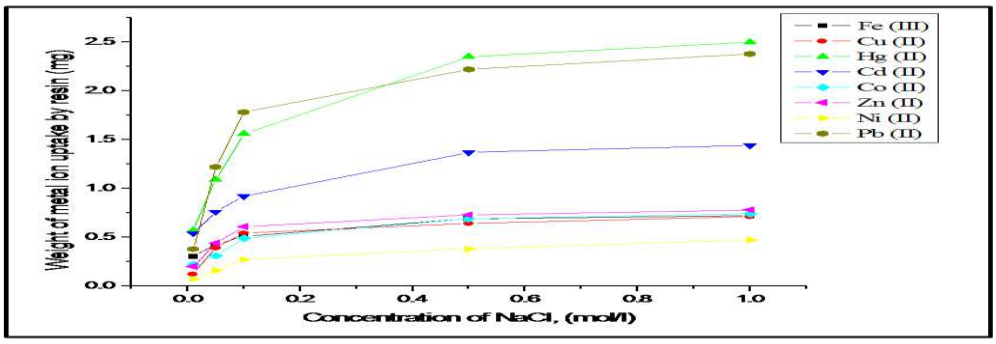


Fig. 6. Evaluation of the influence of different electrolytes on uptake of several metal ions[a] by terpolymer resin at different concentrations of NaCl electrolyte solution.

Fig. 7. Evaluation of the influence of different electrolytes on uptake of several metal ions[a] by terpolymer resin at different concentrations of $NaClO_4$ electrolyte solution.

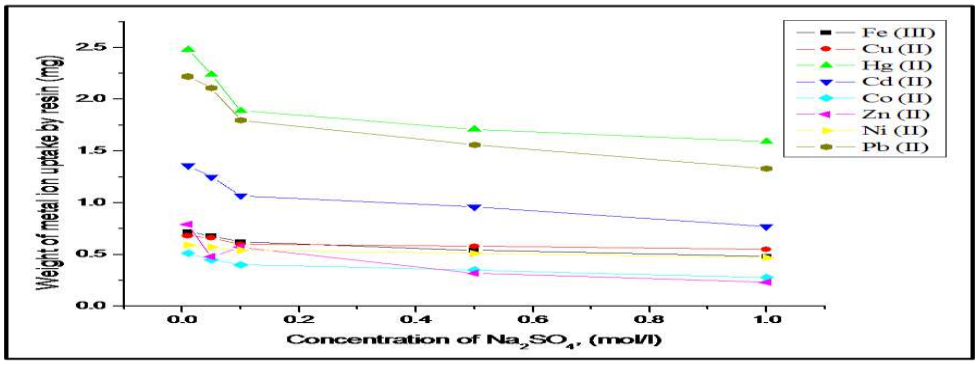


Fig. 8. Evaluation of the influence of different electrolytes on uptake of several metal ions[a] by terpolymer resin at different concentrations of Na_2SO_4 electrolyte solution.

3.2.2 Rate of uptake for metal ions as a function of time

The rate of metal adsorption refers to the change in concentration of metal ions in aqueous solution which is in contact with given polymer and was determined to find out the shortest period of time for which equilibrium could be carried while operating as close to equilibrium conditions as possible. The results are expressed graphically shown in Figure 9, show that the time taken for the uptake of different metal ions at a given stage depends on the nature of metal ion under given conditions. It is found that Fe^{3+} ions required about 3 h for the establishment of the equilibrium, whereas Cu^{2+}, Ni^{2+}, Co^{2+} and Zn^{2+} required 5 h and Hg^{+2}, Cd^{2+} and Pb^{2+} ions required about 7 h. Thus, the rate of metal ions uptake follows the order as $Fe^{+3} > Ni^{+2} > Pb^{+2} > Cu^{+2} \approx Co^{+2} > Cd^{+2} > Zn^{+2} > > Hg^{+2}$ which agrees well with the results reported in literature [19, 20].

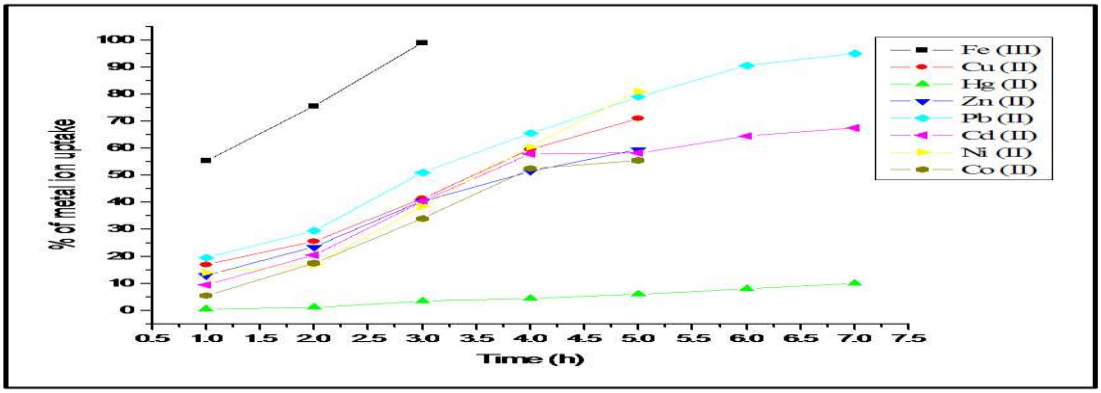


Fig. 9. Comparison of the rate of metal ions[a] uptake[b] by terpolymer, [a] $[M(NO_3)_2]$ = 0.1 mol/l; volume : 2 ml; $NaNO_3$ = 1.0 mol/L; volume: 25 ml, room temperature.

[b] Metal ion uptake = (Amount of metal ion absorbed x 100) / amount of metal ion absorbed at equilibrium.

3.2.3 Distribution ratio of metal ions at different pH

The effect of pH on the amount of metal ions distributed between two phases can be explained on the basis of results shown in Figure 10. The distribution ratio as a function of pH indicates that the relative amount of metal ion taken up by the terpolymer increases with rising pH of the medium, however, the magnitude of increase is different for each metal ion. The study was carried out only up to pH 6.5 in order to prevent hydrolysis of the metal ions at higher pH. In case of Fe^{3+} the highest working pH is 2.5. The terpolymer resin taken up Fe^{3+} ion more selectively than any other metal ions under study. The order of distribution ratio of

metal ions measured in pH range 2.5 - 6.5 is found to be as $Fe^{+3} > Cd^{+2} > Co^{+2} > Zn^{+2} > Cu^{+2} > Hg^{+2} > Pb^{+2} \approx Ni^{+2}$.

Thus, the results of this type of study are helpful in selecting the optimum pH for a selective uptake of a particular metal cation from a mixture of different metal ions [24]. For example, the result suggest the optimum pH 6.0, for the separation of Co^{+2} and Ni^{+2} with distribution ratio 'D' at 3000.0 and 568.90 respectively, using the present terpolymer resin as ion-exchanger. Similarly, for the separation of Cu^{+2} and Fe^{+3} the optimum pH is 3 at which the distribution ratio for Cu^{+2} is 1466.6 and that for Fe^{+3} is 3900.0. The lowering in the distribution of Fe^{+3} was found to be small and hence, efficient separation could be achieved.

In order to assess the utility of present terpolymer resin for the separation of Fe^{3+} ions from other metal ions, the following combinations of metal solutions were prepared: (1) Fe^{3+} and Cu^{2+} (2) Fe^{3+} and Ni^{2+} (3) Fe^{3+} and Co^{2+} (4) Fe^{3+} and Zn^{2+} (5) Fe^{3+} and Cd^{2+} (6) Fe^{3+} and Pb^{2+} etc. The solution for separation studies were prepared by mixing 1ml of 0.1M solutions of Fe^{3+} with 1ml of 0.1M solution of Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+} Hg^{+2} and Pb^{2+}. Selective uptake of the metal ions was studied by adjusting the optimum at pH 3. Distribution ratios of Fe^{3+} at pH 3 in the mixture with metal ions Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+} were found to be 1466.6, 568.90, 3000.0, 2537.0, 3700.0 and 870.70 respectively i.e. slightly lower than 3900.0 found when Fe^{3+} alone was studied. The lowering in the distribution ratios of Fe^{3+} was found to be small and hence efficient separation could be achieved which shows the importance of newly synthesized copolymer resins as an effective ion exchanger and can be explored for the separation of other metal ions.

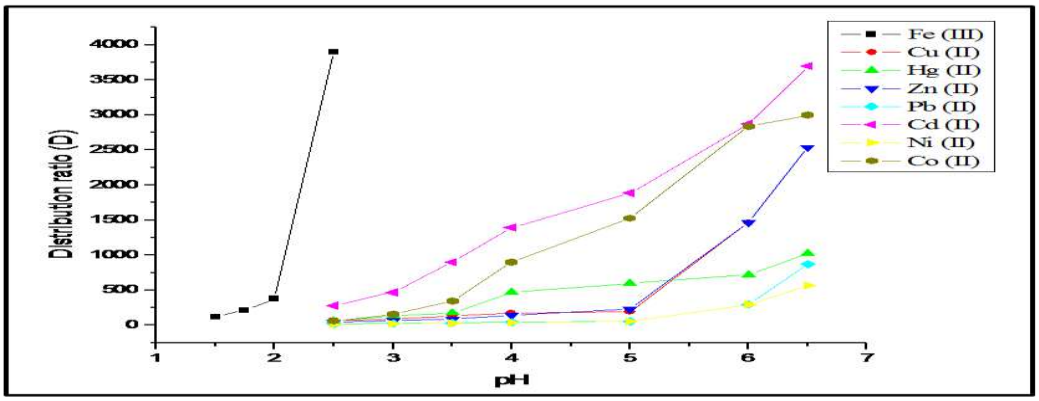


Fig. 10. Distribution ratio, D[a], of various metal ions[b] as function of the pH by terpolymer

[a]D = weight (in mg) of metal ions taken up by 1g of terpolymer/weight (in mg) of metal ions present in 1ml of solution.

[b]$[M(NO_3)_2]$ = 0.1 mol/l; volume : 2 ml; $NaNO_3$ = 1.0 mol/l; volume: 25 ml, time 24 h (equilibrium state) at room temperature.

4. Conclusion

A synthesis of new terpolymer 4,4'-BP-BD-F, based on the condensation reaction of 4,4'-biphenol and benzidine with formaldehyde in presence of acid catalyst was carried out and structure has been confirmed by elemental and spectral studies. It was proved to be selective chelating ion-exchanger for Fe^{3+}, Cu^{2+} Ni^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+} and Hg^{+2} metal ions and has been successfully used for selective separation of ferric ions from other metal ions having combinations like a) ferric and cupric ion b) ferric and mercuric ion c) ferric and zinc ion and d) ferric and lead ion etc. This polymer showed higher selectivity for Fe^{3+} at pH 2.5 as compared to other metal ions.

To explore the use of this chelating resin for the separation of other metal ions in analytical chemistry appears to be advantageous when the separation problem can not be solved

by simpler means or when time can be saved. The area of application especially includes the concentration and the separation of chemically very similar ions. The use of this eco-friendly ion exchanger resin may effectively be explored in hydrometallurgy, antibiotics, purification and separation of radioisotope, in water treatment and pollution control, for the removal of hazardous and toxic metal ions like other ion exchangers.

Acknowledgement

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83

Navigating the Therapeutic Landscape: Discovery and Pharmacophore Modeling of BRD4 Inhibitors for Prostate Cancer Precision Treatment

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Abstract:-

This study represents a ground breaking exploration in the realm of prostate cancer therapeutics by focusing on the identification and optimization of inhibitors targeting Bromodomain-containing Protein 4 (BRD4). The research meticulously navigates the intricacies of BRD4 inhibition with a specific emphasis on tailoring these inhibitors for the treatment of prostate cancer. Employing a multifaceted approach, we delve into the process of identifying novel BRD4 inhibitors, breaking new ground in the field of cancer research. The study's core methodology involves not only the identification and optimization of BRD4 inhibitors but also their customization for precision treatment of prostate cancer. Pharmacophore modelling emerges as a pivotal tool in this endeavour, providing insights into the structural features crucial for effective inhibition. The interplay between innovative drug design and computational modelling techniques promises a refined understanding of the intricate molecular interactions between BRD4 inhibitors and their target. Through a comprehensive analysis, this research aims to contribute to the development of advanced therapeutic strategies for prostate cancer. The outcomes hold the potential to revolutionize precision medicine in the context of cancer treatment, offering new avenues for tailored therapeutic interventions. This study not only breaks new ground in the identification and optimization of BRD4 inhibitors but also paves the way for future advancements in prostate cancer therapeutics through the integration of pharmacophore modelling.

Keywords: Pharmacophore modelling, BRD4, Drug Discovery

1. Introduction:

Bromodomain-containing protein 4 (BRD4) is a crucial regulator involved in transcriptional and epigenetic processes, playing a pivotal role in various cellular functions and diseases. As a member of the BET (bromodomain and extra-terminal domain) family, BRD4 is known for its influence on gene expression and chromatin remodeling [1]. It has been extensively studied in the context of cancer, where it acts as a transcriptional and epigenetic regulator impacting cancer progression and inflammatory diseases [2][1]. Additionally, BRD4 has been associated with angiogenesis and is recognized as a potential therapeutic target for diseases involving abnormal cell growth [3] [4]. The interplay between BRD4 and the MYC proto-oncogene further highlights its significance in both normal development and disease pathogenesis [5].

BRD-4 inhibitors have emerged as promising therapeutic agents in various medical contexts. These inhibitors target the bromodomain-containing protein 4 (BRD-4) and are designed to modulate its activity. Treatment with BRD-4 inhibitors has been shown to reduce the expression of super-enhancer-associated oncogenes like MYC, E2F1, and BCL6, highlighting their potential in cancer therapy [6]. Moreover, BRD-4 inhibition has been associated with impaired DNA mismatch repair, induction of mismatch repair mutation signatures, and the creation of therapeutic vulnerabilities, particularly in immune-related responses [7]. Clinical studies have demonstrated the effectiveness of BRD-4 inhibitors in glioma, where BRD-4 expression is significantly higher than in adjacent normal brain tissue [9]. The development of

these inhibitors has traditionally focused on bromodomains, specifically bromodomain 1 and bromodomain 2, providing insights into potential therapeutic strategies [8].

The objective of the paper is to explore the molecular mechanisms underlying BRD-4 inhibition, focusing on how inhibitors interact with BRD-4 and modulate its activity. Utilize structural and biochemical studies to provide detailed insights into the binding interactions.

2. Methodology:

2.1 SMILES Collection: The SMILES notation provided a compact representation of the chemical structure, and the IC50 values has given an indication of each ligand's potency as an inhibitor, with lower values suggesting higher potency. Researchers have used this information to assess the effectiveness of compounds in inhibiting a specific target, in this case, BRD4.

Sr. No	LIGAND ID	Smiles	IC50nM [10]
1	SQ-9	CN1C2=CC=CC=C2C(OCCCC(NC3=CC=C(F)C=C3)=O)=CC1=O	80.54
2	SQ-17	CN1C2=CC=CC=C2C(OCCCC(NC3CCCCCC3)=O)=CC1=O	95.88
3	SQ-12	CN1C2=CC=CC=C2C(OCCCC(NC3=CC=C(F)C=C3F)=O)=CC1=O	96.33
4	SQ-14	CN1C2=CC=CC=C2C(OCCCC(NC3=CC=CC=C3F)=O)=CC1=O	152.8
5	SQ-19	CN1C2=CC=CC=C2C(OCCCC(NC3=CC=C(C(C)C)C=C3)=O)=CC1=O	254.1
6	SQ-18	CN1C2=CC=CC=C2C(OCCCC(NC3=CC=C(CC)C=C3)=O)=CC1=O	392.6
7	SQ-21	CN1C2=CC=CC=C2C(OCCCC(NC3=CC=CC(C#N)=C3)=O)=CC1=O	585.5
8	SQ-13	CN1C2=CC=CC=C2C(OCCCC(NC3=CC(Cl)=CC=C3OC)=O)=CC1=O	623.8
9	SQ-15	CN1C2=CC=CC=C2C(OCCCC(NC3=CC=CC(OC)=C3)=O)=CC1=O	630
10	SQ-1	O=C3/C=C(/OCCCC(=O)NC=1/C=C(/[Cl])C=CC=1)C2=CC=CC=C2N3C	676.1
11	SQ-10	CN1C2=CC=CC=C2C(OCCCC(NC3=CC=CC(C(F)(F)F)=C3)=O)=CC1=O	1175
12	SQ-11	CN1C2=CC=CC=C2C(OCCCC(NC3=CC=C(C)C=C3Br)=O)=CC1=O	1177
13	SQ-20	CN1C2=CC=CC=C2C(OCCCC(NC3=C(OC)C=C(Cl)C(C)=C3)=O)=CC1=O	1256
14	SQ-8	CN1C2=CC=CC=C2C(OCCCC(NCC3=C(Cl)C=C(F)C=C3)=O)=CC1=O	1650
15	SQ-7	CN1C2=CC=CC=C2C(OCCCC(NCC3=CC=C(F)C=C3)=O)=CC1=O	1688
16	SQ-16	CN1C2=CC=CC=C2C(OCCCC(NC3=CC(Cl)=C(OC)C=C3OC)=O)=CC1=O	1781
17	SQ-5	CN1C2=CC=CC=C2C(OCC(NC3=CC=C(F)C=C3F)=O)=CC1=O	4747
18	SQ-3	CN1C2=CC=CC=C2C(OCC(NC3=CC=C(C)C=C3Br)=O)=CC1=O	5996
19	SQ-4	CN1C2=CC=CC=C2C(OCC(NC3=CC=C(C)C(F)=C3)=O)=CC1=O	9209
20	SQ-6	CN1C2=CC=CC=C2C(OCC(NC3=CC=C(Br)C=C3C)=O)=CC1=O	9307
21	SQ-2	CN1C2=CC=CC=C2C(OCC(NC3=CC=C(F)C=C3)=O)=CC1=O	25748

Note: - Not Determined [10]

Database Selection: Chose a reputable chemical data from literature [10] to collect SMILES notations of target molecules. Data Filtering: Filtered the dataset based on specific criteria, such as biological activity or structural features, to ensure relevance to our study.

2.2. SMILES to 3D Conversion:

Software Selection: Used molecular modeling software like RDKit, Open Babel, or Pybel to convert SMILES to 3D structures using MMFF94 force field. Conversion Process: Utilized the chosen software to convert SMILES notations into 3D molecular structures, ensuring proper handling of stereochemistry and atom coordinates.

2.3. Optimization: Geometry Optimization: Performed energy minimization and geometry optimization on the 3D structures to obtain stable conformations. Tools like RDKit and Open Babel provided optimization functionalities.

2.4. Saving as .SDF File:

File Format Conversion: Saved the optimized 3D structures in the Structure Data File (.sdf) format. Most molecular modeling software tools support this format for saving molecular

information. Consistency Check: Ensured that the saved .sdf file maintains the integrity and consistency of the molecular structures.

2.5. Pharmacophore Generation using PyMOL and Liquid Plugin: Software Installation: Executed PyMOL, a powerful molecular visualization tool, and the Liquid plugin for pharmacophore generation. Opened the saved .sdf file containing optimized structures in PyMOL.

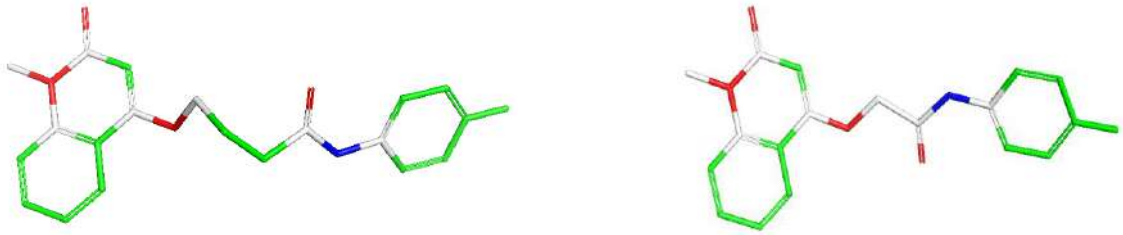
Pharmacophore Generation: Used the Liquid plugin to generate pharmacophores based on specific features such as hydrogen bond donors/acceptors, hydrophobic regions, and aromatic centers. Visualization: Visualized the generated pharmacophores in PyMOL for further analysis.

3. Results and Discussion:

Our research represents a significant stride forward in the pursuit of enhanced therapeutics for prostate cancer. The systematic identification and optimization of BRD4 inhibitors, underscored by the innovative integration of pharmacophore modeling, have collectively marked a breakthrough in precision medicine for cancer treatment. The tailored design and optimization of these inhibitors exhibit a promising avenue for addressing the unique challenges posed by prostate cancer.

Through a meticulous exploration of molecular interactions and structural features, this study provides valuable insights that contribute to the refinement of BRD4 inhibitors. The potential impact of these findings extends beyond the laboratory, offering a blueprint for the development of targeted therapies in the clinical setting. The fusion of cutting-edge drug design strategies with computational modeling techniques not only breaks new ground but also lays a foundation for the evolution of personalized treatment approaches.

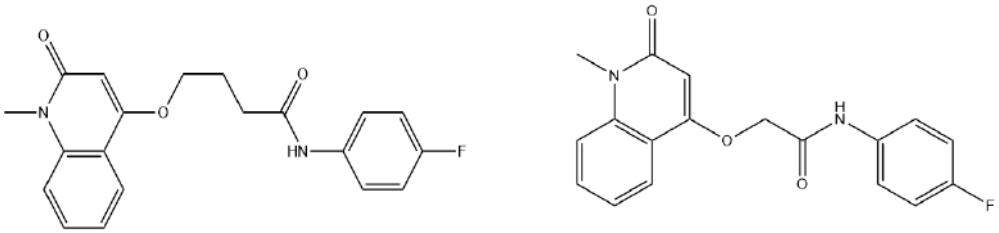
As we move forward, the outcomes of this research hold the potential to reshape the landscape of prostate cancer therapeutics. By breaking new ground in the identification and optimization of BRD4 inhibitors and harnessing the power of pharmacophore modeling, we chart a course towards more effective and tailored interventions. This study serves as a catalyst for future advancements, fostering a paradigm shift in the way we approach precision medicine for prostate cancer and potentially other malignancies.



SQ-9
Most active

SQ-2
Least active

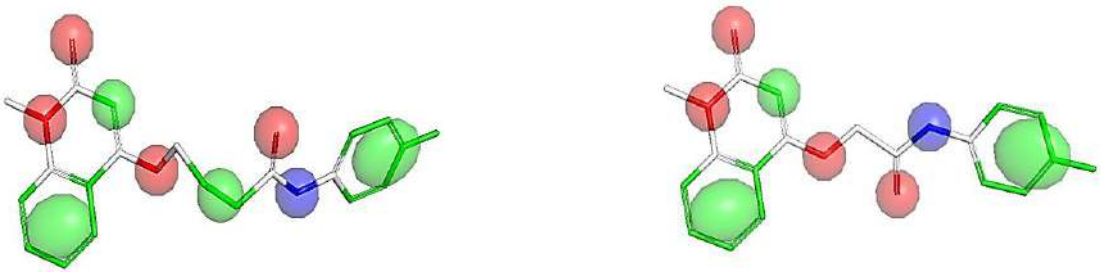
Figure3.1: - 3D Structure of most active and least active molecules, with distorted geometry of molecules.



SQ-9
Most active

SQ-2
Least active

Figure3.2: - 2D Structure of most active and least active molecules.



SQ-9 SQ-2

Most active molecule Least Active molecule

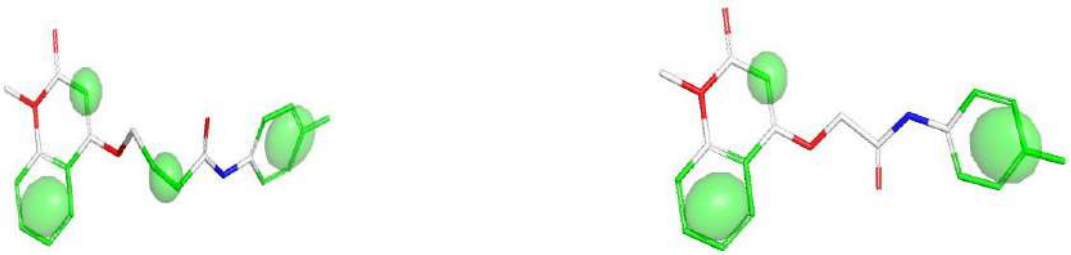
Figure3.3: - Above figure shows the pharmacophore model structure of most active and least active molecules.

Pharmacophore modelling green colour for lipophilic, blue colour for H-donor and red colour for H-acceptor. In this figure SQ-2 structure shows three lipophilic, four H-acceptor and one H-donor molecules. In SQ-9 structure four lipophilic, four acceptor and one donor molecules.



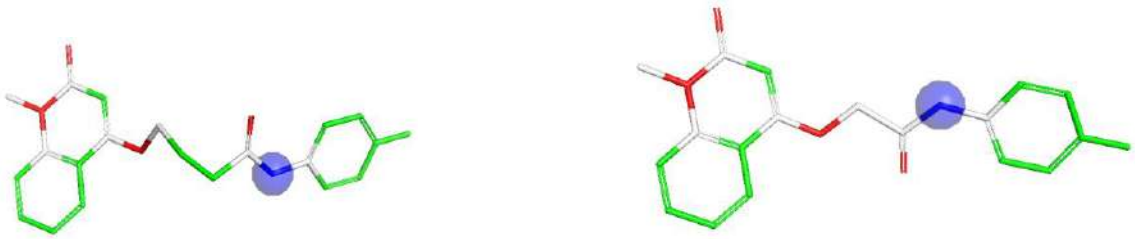
SQ-9 SQ-2

Figure 3.4: - In this above structure SQ-9 and SQ-2 both showing Same Number of H-acceptor



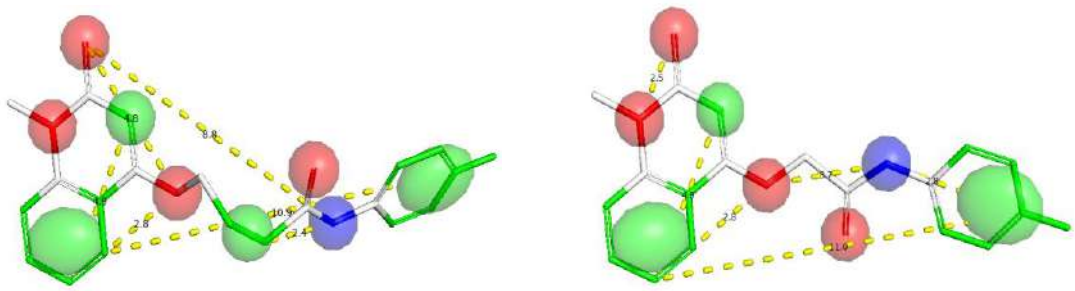
SQ-9 SQ-2

Figure 3.5: - SQ-9 having four lipophilic parts and SQ-2 having only three lipophilic part in this figure.



SQ-9 SQ-2

Figure 3.6: - In this above structure SQ-9 and SQ-2 both showing Same Number of H-donor (one H-Donor)



SQ-9 SQ-2

Figure3.7: - Measure distances between Lipophilic, H-acceptor and H-donor in most active and least active molecules.

In the SQ-9 shows distorted geometry with four lipophilic parts, the lipophilic to lipophilic higher distance is 10.9A^0 and lowest distance is 4.9A^0, H-acceptor to H-acceptor distance is 4.2 A^0, H-acceptor-Lipophilic distance is 2.8 A^0 and H-acceptor to H-donor distance is 8.8A^0. The SQ-2 having only three lipophilic parts in the molecule, in this structure lipophilic-lipophilic higher distance is 11.0A^0 and lipophilic to lipophilic lowest distance is 4.9A^0, H-acceptor to H-acceptor distance is 2.5 A^0, H-acceptor to Lipophilic distance is 2.8 A^0, and H-acceptor to H-donor distance is 3.7A^0.

Conclusion:-

In conclusion, our research represents a significant stride forward in the pursuit of enhanced therapeutics for prostate cancer. The systematic identification and optimization of BRD4 inhibitors, underscored by the innovative integration of pharmacophore modeling, have collectively marked a breakthrough in precision medicine for cancer treatment. The tailored design and optimization of these inhibitors exhibit a promising avenue for addressing the unique challenges posed by prostate cancer. Through a meticulous exploration of molecular interactions and structural features, this study provides valuable insights that contribute to the refinement of BRD4 inhibitors. The potential impact of these findings extends beyond the laboratory, offering a blueprint for the development of targeted therapies in the clinical setting. The fusion of cutting-edge drug design strategies with computational modeling techniques not only breaks new ground but also lays a foundation for the evolution of personalized treatment approaches.

As we move forward, the outcomes of this research hold the potential to reshape the landscape of prostate cancer therapeutics. By breaking new ground in the identification and optimization of BRD4 inhibitors and harnessing the power of pharmacophore modeling, we chart a course towards more effective and tailored interventions. This study serves as a catalyst for future advancements, fostering a paradigm shift in the way we approach precision medicine for prostate cancer and, potentially, other malignancies.

"Sincere acknowledgement to Prof. Dr. Vijay H. Masand for his support throught the research work."

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84

Synthesis and Characterization of Novel Activated Carbons derived from different parts of Abutilon Indicum plant by using $ZnCl_2$ activating agent

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Abstract:
Fine powdered novel activated charcoals were synthesized from different parts (Root, Stem, Flower and leaves) of plant Abutilon Indicum by known method. Carbonization was done at 300°C for one hour and allowed to cool at room temperature. After washing chemical activation was carried out by impregnating the synthesized charcoal with activating agent $ZnCl_2$ and heated to 500°C for one hour. Synthesized four novel activated carbons were characterized by FTIR and further studied with respect to FTIR of their corresponding precursors.
Keywords: Abutilon Indicum, Carbonization, Activation.

Introduction:
Biomass wastes were inexpensive and renewable abundantly occured in nature. From these waste biomass the manufacturing of products is great interest of researchers. Researchers derived activated carbons from these renewable sources like plant, trees, grasses and their parts roots, fruit peels, stem leaves. However, in todays sinario synthsis of activated carbon from renewable sources is is a great intrest and fascinating because it is sustainable and ensuring the balance between environment and economic growth.[1] Activated carbon (AC) and Activated charcoal are same things having porous carbonaceous nature along with large surface area. AC is solid, , micro-crystalline, tasteless and non-graphitizable form of carbon black. It can be synthesized from the carbon rich species after carbonization of carbon rich material. Due to the remarkable adsorption characteristics with versatile adsorbent capacity. The adsorption characteristics of activated charcoal depend on the size of particle, precursor type, and the method used for the preparation. The quality of adsorption of the activated charcoal is affected by the activation time, carbonization temperature, activating reagent and presence of impurities.[2-8] AC is having high surface area and porosity. The surface area up to 3000 m^2/g of the adsorbent pores formation and the functional groups are tuned by the process of activation facilitating the adsorption of pollutants. Because of the fast adsorption and ease of regeneration, activated charcoal used as an adsorbent[9].

The first use of activated charcoal in the form of wood char goes to Egyptian and Sumerian's ancient records in 3750 BC. where it was used for smelting ores to create Bronze, adsorption of unpleasant odour. According to Hindu literature (400 BC), drinking water from sources was filtered by sand and charcoal. In the time of Hippocrates, charcoal of wood was used for medicinal purposes. In (157BC) carbon derived from animal and vegetable origin was used to cure diseases. The adsorptive power of charcoal using adsorption of uses on the surface of charcoal was first recognized in 1773 by Scheele. The application of charcoal by using charcoal in various aqueous solutions for the decolonization was studied in 1788 by Lowitz. Later Kehl, in 1793 recognized that the activated carbon derived from animal tissue used for the decolorization. During those days, An English sugar company derived activated charcoal from wood in 1794 and used it for colour removal of sugar syrup. Gradually the use of bone char for decolorization increases instead of using wood char and in 1817 it had been proved that bone char was more effective than wood char. In 1900 Osterjko introduced criteria of activation and patented about adsorbing power of the Charcoal.In 1911 using osterjko method,

the first commercially activated charcoal manufactured and marketed with the trade name Epoint for sugar refinery companies as decolorizer. Commercially AC produced from sawdust using $ZnCl_2$ as an activating agent.[10-14]

Commercial activated charcoal prepared by using precursors which are highly costly and non-renewable sources such as petroleum, wood, coal and peat. Activated carbon has an application in the separation and purification of liquid or gas as it acts as an adsorbent. The high performance layer capacitors are manufactured by using highly porous activated carbon this is being the application of activated charcoal as an adsorbent. Because of the development of new application, the demand for the porous carbon increase progressively. Adsorption is a surface process that leads to transfer of molecule from a fluid bulk to solid surface. This can occur because of physical forces or by chemical bonds.[15] Due to increasing demand of activated carbon, there is a strong need for sorting out new precursors for the preparation of activated charcoal which should be commercially available and cost effective. This demand can be met by utilizing locally available raw material, agricultural waste, biomass for the preparation of activated carbon. In this regard, the organic waste biomass, is the best choice for the synthesis of activated charcoal.[16]

Materials and Methods:

A) Sample collection and preparation.

The material which belongs to plant origin show high carbon content and low ash content. In present study abitilon indicum used for the preparation of activated charcoal it was collected from different farms which are 10 km away from Malkapur. The different parts of abutioln indicum material like roots, stem, leaves and flower were washed thoroughly with water in order to remove the foreign content. After washing all material were sun dried for 4 to 5 days. After sun drying materials were ground into a fine powder using mortar and pestle. Befor carbonization the moisture of material removed by heating at 110 ^oC for an hour in hot air oven.

B) **Carbonization and Activation**

Carbonization of well dried sample was then carried out in a muffle furnace (Bio-techno Lab, Model AI 7081) by placing a sample in a silica crucible at temperature of 300 ^0C for one hour each. It was ensuring absence of oxygen during carbonization. The charcoal thus produced was removed from the furnace, washed with water after cooling and dried at 110 ^0C and ground with help of mortar pestle by applying moderate pressure. Further sieved through 100-200 mesh. Finally chemical activation was done according to the methods of Grigis et al method with slight modification. The aqueous solution of Zinc Chloride ($ZnCl_2$) was mixed with 25 g sample in the ratio 1:5 the mixture was soaked for twelve hours and later heated to form a paste. The paste was placed in the furnace and carbonized at 500 ^0C temperature for one hour. The sample was cooled to room temperatur overnight. Futher washed with the distilled water and dried at 110 ^0C in an oven and allow to cool at room temperature. The AC produced was sieved with 106 µm mesh, kept in an air tight bottle and labelled as follows.[17]

Result and Discussion:

Sr. No.	Sample Name	Code for Raw Samples	Code for Activated sample	Activation Method
1	Abutilon Indicum Flower	AIFR	AIFAC500	Chemical activation by using 1N $ZnCl_2$ at 500 ^0C
2	Abutilon Indicum Leaves	AILR	AILAC500	
3	Abutilon Indicum Stem	AISR	AISAC500	
4	Abutilon Indicum Root	AIRR	AIRAC500	

Table :1 List of sample collected and synthesized activated carbons with their code.

Sr.No.	Possible assignments (Precursors)	Abutilon Indicum Flower (Raw Sample)	Abutilon Indicum Leaves (Raw Sample)	Abutilon Indicum Stem (Raw Sample)	Abutilon Indicum Root (Raw Sample)
1	O-H str, -NH	3724,3650cm^{-1}	3643 cm^{-1}	3730, 3596cm^{-1}	3650
2	C-H in -CH_3 and -CH_2	2978, 2889	2981, 2883	2786	2825
3	-C=O Str	1600 cm^{-1}	1637, 1539 cm^{-1}	1641 cm^{-1}	1615 cm^{-1}
4	Aromatic -C=C-	1386cm^{-1}	1539 cm^{-1}	1424 cm^{-1}	1317 cm^{-1}
Sr.No.	Possible assignments (Activated carbons)	Abutilon Indicum Flower (AIFAC 500)	Abutilon Indicum Leaves (AILAC 500)	Abutilon Indicum Stem (AISAC 500)	Abutilon Indicum Root (AIRAC 500)
1	O-H str	3725, 3800 cm^{-1}	3660 cm^{-1}	3631 3784 cm^{-1}	3659 cm^{-1}
2	C-H in CH_3 and CH_2	2981, 2882 cm^{-1}	2979, 2885cm^{-1}	2886cm^{-1}	2887cm^{-1}
3	-C=O Str	--	--	--	--
4	Aromatic C=C	1428 cm^{-1}	1397 cm^{-1}	1436 cm^{-1}	1441 cm^{-1}

Table:2 Shows the IR characterization of raw samples and activated carbons activated by zinc chloride.

FTIR spectra were used to characterize the surface functional group on the flower AIFR, the root AIRR and troot and the Acs prepared from these precursors. Table 1 shows the list of sample collected and synthesized activated carbons with their code.Table 2 shows the absorption peaks observed in precursors and absorption peaks observed in corresponding Acs. The precursors AIFR, AILR, AISR and AIRR contained absorption band for carbonyl stretch and the same absorption bands were absent in their corresponding synthesized Acs AIFAC500, AILAC500, AISAC500 and AIRAC500 indicating that the chemical activation brok many bonds in aliphatic and aromatic species with elimination of many lite and volatile substrate.[18]

The C-H vibration in methyl and methylene groups at 2881, 2882 cm^{-1} in AIFAC500, 2979, 2885 cm^{-1} in AILAC500, 2886 cm^{-1} AISAC500, 2887cm^{-1} AIRAC500 becomes much weaker after activation, suggesting that carbinization of material is almost completed.[19]

Almost in all newly synthsized activated carbons absorption band intensity decreses dramatically shows the decrease in functionality in the main matrix of raw material.

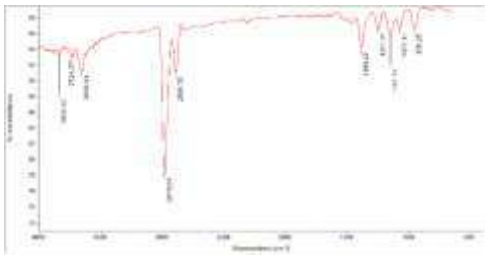


Figure 6 AIFR

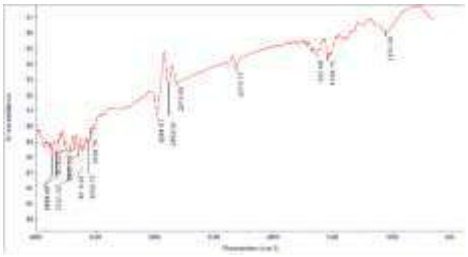


Figure 7 AILR

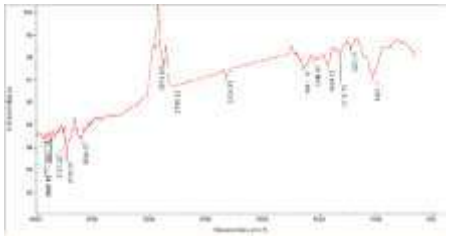


Figure 8 AISR

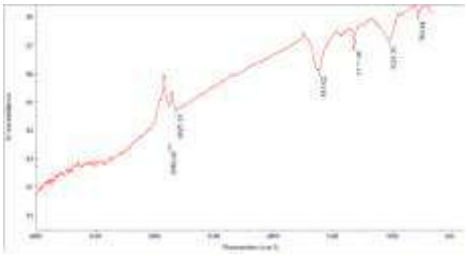
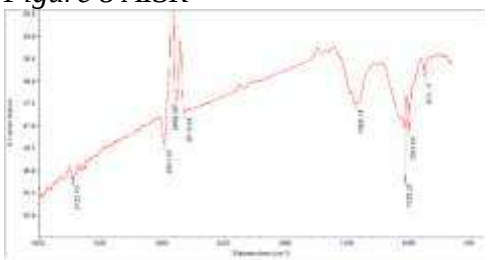
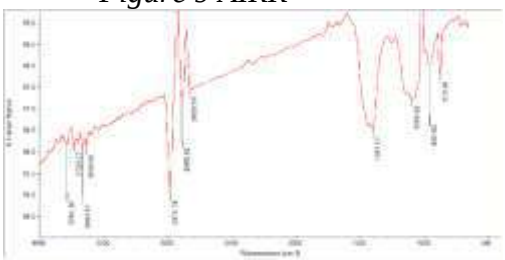


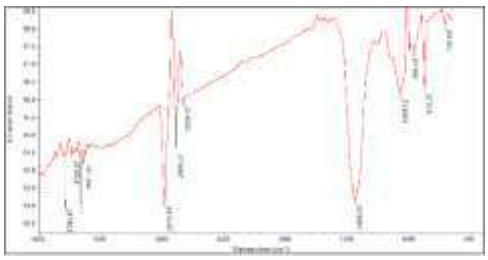
Figure 9 AIRR



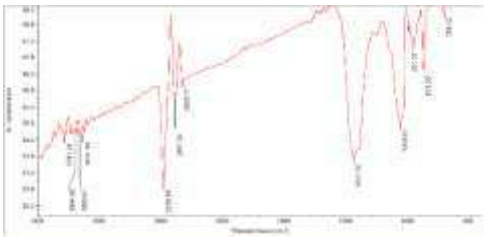
1- AIFAC500



2-AILAC500



3-AISAC500



4-AIRAC

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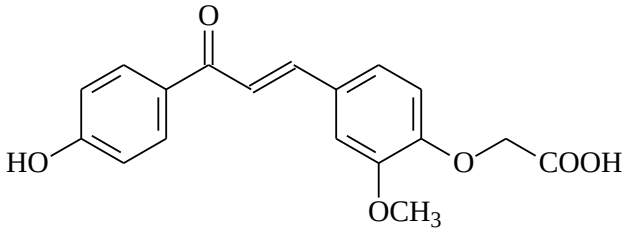
85

A Review Study on pyrazole containing flavones by using Green Solvents

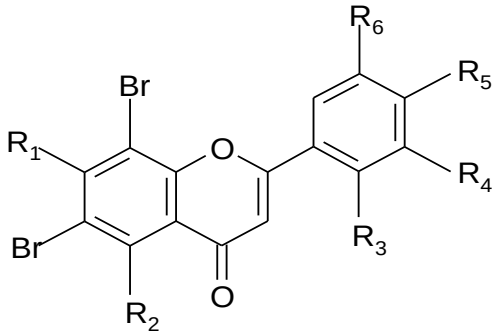
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Introduction:

Chalcones are heterocyclic compounds of unsaturated ring structure having pyrazole moiety several chalcones derivatives possess important pharmacological activities and therefore they are useful materials in drug research. Chlacones are biologically active scaffolds with a variety of biological activities like antimicrobial [1], antitubercular [2], anti-inflammatory [3], anticancer [4], antitumor [5], anticonvulsant [6], and anti-HIV [7]. Flavoniods are grouping of polyphenolic compound that occur naturally in foods of plant origin. These compound possess a common structure and they are categorized according to the saturation level mainly into flavones,flavanols and flavanones on the other hand Flavones have useful biological activites such as antioxidant [8], anxiolytic[9] ,anticancer[10], analgesic and anti-inflammatory [11,13] antimicrobial [14],antiulcer and thrombosis [15]. Mohammad Shahar[16] *et al.* reported a series of chalcones by the condensation of 2-(4-formyl-2-methoxy phenoxy) acetic acid with various ketones in methanolic KOH solution. These corresponding chalcones were reacted with appropriate acid hydrazide in glacial acetic acid led to the formation of phenoxy acetic acid derivatives and were evaluated for their anti-mycobacterial activities against Mycobacterium tuberculosis $H_{37}Rv$.



Among the naturally occurring oxygen heterocycles, 2-phenyl-4*H*-1-benzopyran-4-ones (flavones) are important and abundant group of flavonoids. They possess a unique importance, as about 300 different compounds of this class have so far been isolated from natural sources and thousands of their derivatives have been synthesized. Abu T. Khan[45] *et al*. have synthesized various ring substituted 6, 8-dibromoflavones as well as 8-bromoflavones easily from the corresponding 2'-hydroxychalcones in good yields and in two steps under environmentally benign reaction conditions.



Naseem Ahmed[17] *et al*. reported that the silica gel supported $InBr_3$ or $InCl_3$ were explored as a new solid-support catalyst for the facile and efficient cyclization, under solvent-free conditions of 2'-hydroxychalcones and flavanones to yield the corresponding flavones in

> 80% yield. Y. W. Kim[18] *et al.* synthesized and aromatase inhibitory activity of novel pyridine containing isoflavones.

Gil-Izquierdo[19] *et al.* have reported that influence of industrial processing on orange juice flavanone solubility and transformation to chalcones under gastrointestinal conditions. H Wang Eui Il[20] *et al.* have produced of plant-specific flavanones by *Escherichia coli* containing an artificial gene cluster. Kumar Arun[21] *et al*. reported that the natural products such as hydroxy flavanones as antimalerial agents have been discussed in the review. Higuchi Tomihiko[22]*et al.* discovered pharmaceutical compositions and disinfectants containing flavonoids for treatment of drug-resistant bacterial infection. Sairafianpour Majid[23] *et al.* Novel isoflavones were isolated from *Smirnowia iranica*. The isoflavones significantly inhibited the growth of extra-cellular stages of three Leishmania species *in vitro*, their activity against the intracellular stages being considerably lower.

Flavones as an important and abundant group of flavonoids have been synthesized, among various methods, by the oxidative cyclisation of 2'-hydroxy chalcones. These various methods are of limited application as in some of these procedures, the yields are not satisfactory, while some procedures gave a mixture of side products containing flavone, flavanone. Dimethyl sulfoxide (DMSO) is known to facilitate the reaction in different ways when used as reaction medium. As DMSO was used as reaction medium for the cyclisation of 2'-hydroxychalcones with iodine. But sometimes impure DMSO at higher temperature during heating period gets decomposed. Therefore, it reduced yield of product.

General experimental procedure for the synthesis of chalcones

Equimolar mixture of substituted acetophenone (1 mmol), and aromatic aldehyde (1 mmol) was mixed in 15 mL in ethanoltaken in 100 mL conical flask. Then 2-3 mL of saturated solution of KOH (aprox 40%) was added into the flask. The solution becomes reddish brown color. The reaction mixture was kept for overnight at room temperature. On the next day morning, the completion of the reaction was monitored by TLC. After completion of the reaction, then the contents of the flask were poured into 50 mL ice cold water. The corresponding solid was separated then filtered. The crude product was recrystalized from suitable solvent.

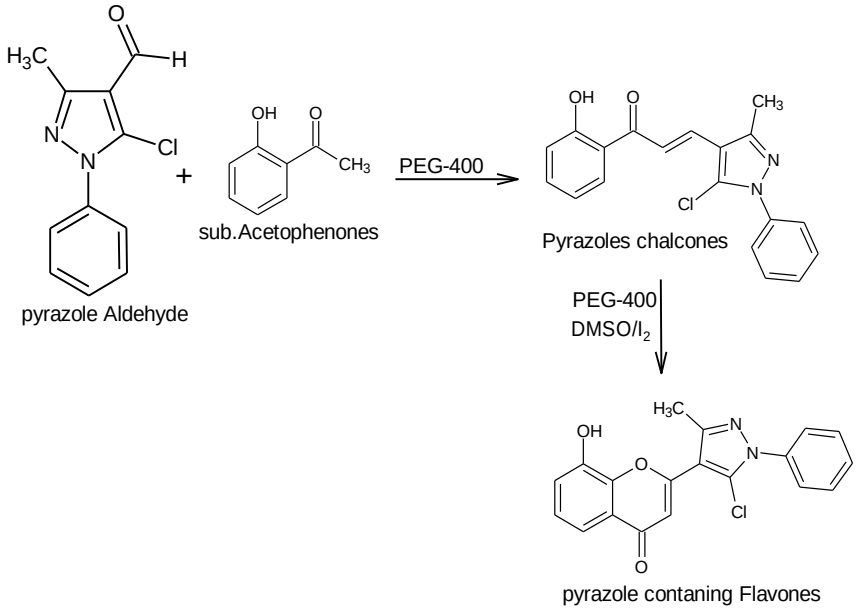
General experimental procedure for the synthesis of Flavones 2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-8-hydroxy-4*H*-1-benzopyran-4-one Equimolar mixture of substituted Chalcone (1 mmol), and DMSO/I_2 (6 mmol) was mixed in 15 mL in PEG taken in 100 mL conical flask. The catalytic amount of I_2 was added to the reaction mixture and heats the content for 30 minute in presence of PEG-400. The reaction completion was indicated by TLC .the reaction was worked up the mixture was poured onto crushed ice and excess I_2 was removed by slow addition of sodium thiosulphate solution the precipitated product was filtered by suction and solid was recrystalized from dilute ethanol to get crystalline flavones. Similarly, all the compounds were synthesized by the same procedure.

Green solvent PEG-400 One of the key areas of green chemistry is the replacement of the hazardous solvent as with environmentally benign solvents like polyethylene glycol (PEG-400). In recent years polyethylene glycol (PEG-400) attracted the much more attention recently, liquid polymers or low melting polymers have emerged as alternative green reaction media with unique properties such as thermal stability, commercial availability, non-volatility, immiscibility with a number of organic solvents and recyclability. PEGs are preferred over other polymers because they are inexpensive, completely non-halogenated, and easily degradable. Flavonoids are substances endowed with a wide number of pharmacological activities.

This method is an efficient and convenient has following merits.

I] PEG is an economically beneficial reaction medium rather than DMSO and other organic solvents.

II] Procedure is green and environmentally benign.
III] Excellent yields and purity of the products are obtained.
IV] Product does not decomposed by this method.
V] Work-up and isolation is easier.
VI] PEG acts as a phase transfer catalyst in organic synthesis



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86

A Review of Supramolecular Chemistry: Unlocking a Promising Future

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Abstract

Supramolecular chemistry, with its focus on non-covalent interactions and molecular self-assembly, has emerged as a dynamic and interdisciplinary field with profound implications across various scientific domains. This research paper presents a comprehensive review of the current state of supramolecular chemistry, exploring its key principles, recent advancements, and the promising future it holds in diverse applications.

Introduction

Supramolecular chemistry involves the study of non-covalent interactions, such as hydrogen bonding, π-π stacking, and van der Waals forces, leading to the spontaneous formation of complex molecular structures. This introductory section highlights the fundamental principles of supramolecular chemistry and its significance in creating functional materials and devices.Tracing the historical development of supramolecular chemistry provides insights into its evolution. From the pioneering work of Jean-Marie Lehn, Donald J. Cram, and Charles J. Pedersen, to the Nobel Prize recognition in 1987, this section outlines the key milestones shaping the field.

Introduction: Supramolecular chemistry is a dynamic field of study that focuses on the interactions between molecules and the assembly of molecular architectures. This essay aims to evaluate various applications of supramolecular chemistry from the perspective of a college student, highlighting its vast potential in diverse areas such as drug delivery, materials science, sensors, and nanotechnology.Important concepts advanced by supramolecular chemistry include molecular self-assembly, molecular folding, molecular recognition, host–guest chemistry, mechanically-interlocked molecular architectures, and dynamic covalent chemistry.

1. Drug Delivery: The ability of supramolecular chemistry to assemble functional systems with controlled release properties has revolutionized drug delivery. By utilizing host-guest interactions and self-assembly, supramolecular carriers can effectively encapsulate drugs, enhance their solubility, and achieve targeted delivery, thus improving therapeutic outcomes while minimizing side effects.

2. Materials Science: Supramolecular chemistry offers a versatile approach to fabricating novel materials exhibiting advanced properties. Through self-assembly, researchers can create hierarchical structures, such as supramolecular polymers, gels, and crystals, with tunable mechanical, optical, and electrical properties. Such materials have applications in energy storage, electronics, and tissue engineering.

3. Sensors: Supramolecular sensing systems exploit molecular recognition to detect analytes with high sensitivity and selectivity. Supramolecular receptors can be designed to recognize specific molecules or ions, enabling the detection of pollutants, toxins, and even biomarkers indicative of diseases. This field holds promise for creating portable and affordable diagnostic tools with applications in healthcare and environmental monitoring.

4. Nanotechnology: Supramolecular chemistry plays a pivotal role in the emerging field of nanotechnology. By utilizing self-assembly, researchers can fabricate functional nanostructures with precise control over size, shape, and functionality. These nanostructures

find applications in areas such as drug delivery, catalysis, imaging, and electronic devices, revolutionizing various industries.

5. Molecular Machines: Supramolecular chemistry has enabled the construction of molecular machines capable of performing mechanical functions at the molecular level. Utilizing controlled molecular motion and coordination principles, these machines have the potential to revolutionize fields such as information storage, artificial intelligence, and even medical diagnostics and treatment.

6. Biomimetic Systems: Inspired by natural systems, supramolecular chemistry allows researchers to develop biomimetic materials and systems. By mimicking natural self-assembly processes, supramolecular chemistry enables the development of artificial proteins, biomaterials, and synthetic cells, opening up new avenues for understanding biological systems and addressing challenges in regenerative medicine.

7. Catalysis: Supramolecular catalysts offer efficient and selective approaches to catalytic transformations, suiting industries such as pharmaceuticals, materials, and energy. The precise positioning of catalysts using supramolecular scaffolds enhances their activity, selectivity, and recyclability, contributing to sustainable chemical processes.

8. Supramolecular Electronics: The ability to self-assemble molecular electronic devices has brought about exciting advancements in supramolecular electronics. Through the precise arrangement of functional molecules, researchers can fabricate nanoscale electronic components like molecular wires, switches, and transistors. These advancements may lead to the development of faster, smaller, and more energy-efficient electronics.

9. Environmental Applications: Supramolecular chemistry can contribute to environmental sustainability by addressing crucial challenges. For instance, supramolecular frameworks can remove heavy metals from contaminated water, while supramolecular sensors enable the detection of harmful substances in the environment. These applications pave the way for environmentally friendly solutions to global issues.

Conclusion: Supramolecular chemistry is a flourishing field with a wide range of applications, demonstrating its potential to revolutionize multiple industries. As a college student, understanding the advancements and potential of supramolecular chemistry allows us to appreciate the diverse possibilities it offers, fostering innovation and contributing to a sustainable future.

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87

Antimicrobial Screening Of Schiff Base (E)-N1-((5-Methylfuran-2-Yl) Methylene)-5-Nitrobenzene-1,2-Diamine Against E. Coli

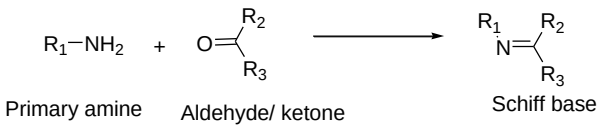
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ABSTRACT
Schiff base (E)-N1-((5-methylfuran-2-yl) methylene)-5-nitrobenzene-1,2-diamine is prepared by condensing 5-methyl 2-furanaldehyde with 4-nitro-o-phenylenediammine containing azomethine group. Synthesized compound is characterized by using spectroscopic tools. Antimicrobial activity of prepared Schiff base is screened against bacterial strain *E. coli* by using disc diffusion method using ceftriaxone as standard. Schiff base shows no activities against bacterial stain *E. coli.*

KEYWORDS- Schiff Base, Synthesis, Characterization, Antimicrobial activity, Disc diffusion method, E. Coli.

INTRODUCTION

Schiff bases, named after Hugo Schiff are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions[1]. Schiff base is a nitrogen analogue of a ketone or aldehyde in which the carbonyl group (C=O) has been replaced by an imine or azomethine group(-C=N-). In these molecules, (-C=N-) group serves a specific purpose in producing these molecules with extensive biological actions on varying R_1, R_2 or R_3 group which can be an H /aryl /alkyl/ heteroaryl group. [2] Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituent are relatively unstable.



Where R_1 and R_3 = alkyl/ aryl/ hetroaryl
R_2 = H , alkyl, heteroaryl

Structural variation in Schiff base allows the researcher to explore its potential application. This is evident from the number of reviews published on the synthesis, structure and application of Schiff base [3–5] including energy materials, [6] antimicrobial studies. [7]

The imine group (CH=N) of Schiff base is a key structural part which is found in various natural compounds of biological significance. Schiff bases shows prominent biological activities such as antimicrobial, [8] antiproliferative [9] and anti-inflammatory [10] properties. Furanoid group containing Schiff bases shows enhanced antimicrobial activities. [11] In this research paper Schiff base (E)-N1-((5-methylfuran-2-yl) methylene)-5-nitrobenzene-1,2-diamine screened against bacterial strain *E. coli* by disc diffusion method.

MATERIAL AND METHOD

Material

Chemicals were bought from Merck, TCI, Sigma-Aldrich and used without further purification. TLC were performed on precoated aluminium silica gel plates. All reactions were monitored by TLC. Antimicrobial activities of Schiff bases are screened against bacterial strain *E. coli* by disc diffusion method by using ceftriaxone as standard

Method

4-nitro-*o*-phenylenediammine and 5-methyl furfural are mixed together in stoichiometric ratio reaction mixture in methanol was refluxed at controlled temperature, reaction mixture was cooled precipitate obtained was washed by methanol, diethyl ether, hexane and dried in desiccator. Antimicrobial activity will be screened by using disc diffusion method, incubation on standard culture media for 24 hrs at 37^0C for interpretation.

RESULT AND DISCUSSION

In the present study, we carried out experiments to investigate the antimicrobial activity of compounds (E)-N1-((5-methylfuran-2-yl) methylene)-5-nitrobenzene-1,2-diamine was screened for their antibacterial activity against gram-negative bacteria *E. coli* by the disc diffusion method in Mueller-Hinton agar medium at concentrations10,5,2.5,1.25,0.625 and 0.313 mg/ml in DMSO as solvent. These solutions were added to each filter disc, and the plates were incubated at 37 °C and examined for zone of inhibition around each disc after 24 hours. Results were compared with the activity of the standard antibiotic ceftriaxone. According to preliminary antibacterial screening by the paper disc method, compounds (E)-N1-((5-methylfuran-2-yl) methylene)-5-nitrobenzene-1,2-diamine was found to be inactive against bacterial strain *E. coli.*

CONCLUSION

Comparison of result of Schiff base (E)-N1-((5-methylfuran-2-yl) methylene)-5-nitrobenzene-1,2-diamine with standard ceftriaxone, it was found that Schiff base was inactive against bacterial strain *E.coli.*

ACKONWLEDGEMENT

Authors are thankful to consultancy microbiology Department of Microbiology S. G. B. Amravati University Amravati for antimicrobial screening.

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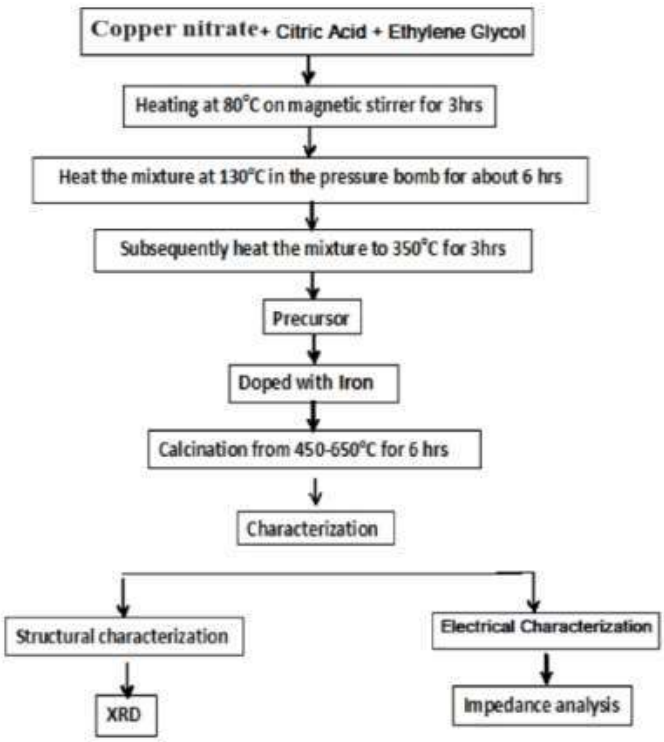
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Effect of Fe Dopant on Structural & Electrical Properties of Copper Oxide Nanoparticles

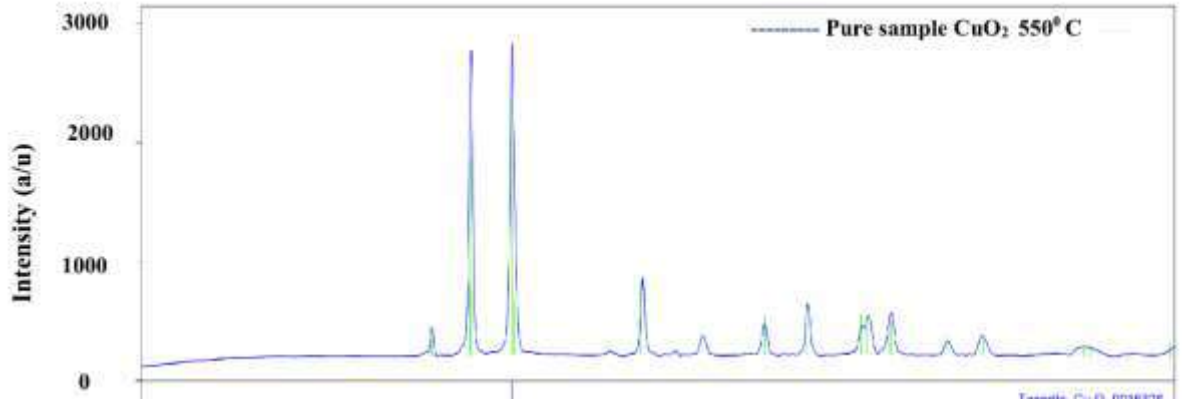
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Abstract:
Nanocrystalline Copper oxide (CuO_2) was synthesized by sol-gel citrate method. Further it was modified by doping Fe in it. Structural and Electrical study was carried out for modified and unmodified CuO_2. From X-ray diffraction (XRD) studies it was observed that when CuO_2 doped with 2% Fe its Average Crystallite Size Increases from 41.32 nm to 54.51 nm on further doping with 0.1% & 0.3% Fe Its Average Crystallite Size decreases to 34.15 nm & 31.35 nm respectively. The electrical study of the nanocrystalline Copper Oxide is checked for different doping amount and also at different temperature for every sample. From the study it is observed that, 0.1 & 0.3 % Fe dopant conductivity changes with the concentration of dopant and also varies with temperature.
Keywords: Copper oxide, X-ray diffraction, crystallite size, Electrical Properties & Conductivity.

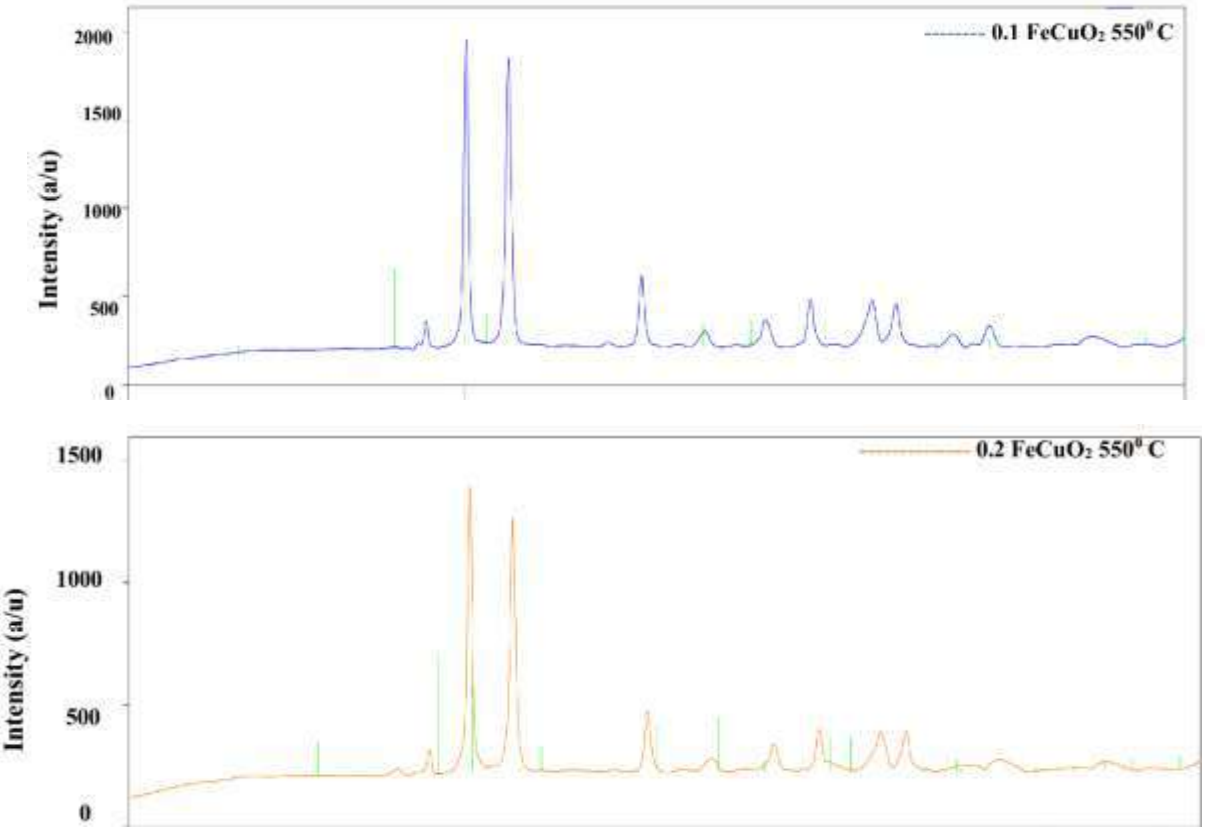
Methodology



Result and discussion:
X-ray Diffraction

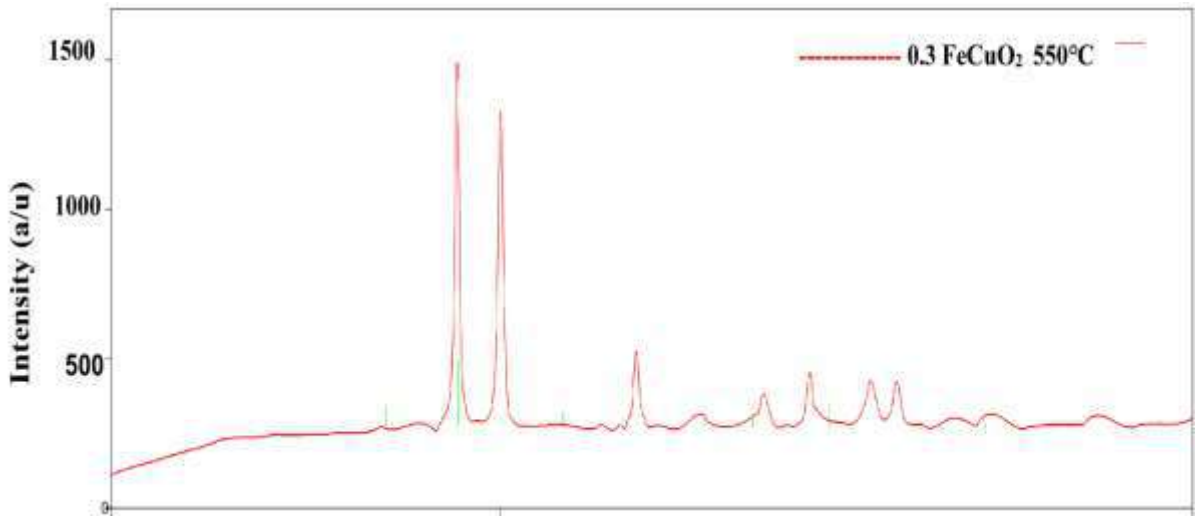


(a)



(b)

©



(d)

Figure 1: XRD plot for a) CuO_2, b) 0.1 % Fe doped CuO_2, c) 0.2 % Fe doped CuO_2, d) 0.3 % Fe doped CuO_2

Impedance Analysis

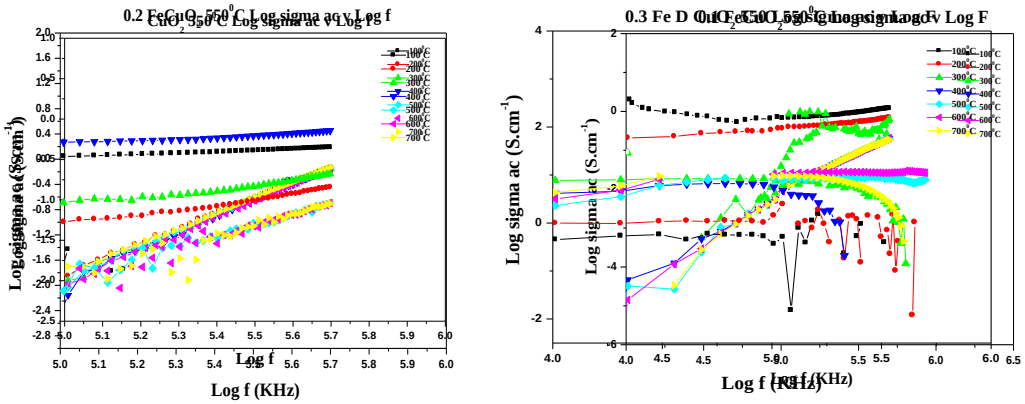


Figure 2:- variation of ac conductivity with frequency for a) CuO_2, b) 0.1 % Fe doped CuO_2, c) 0.2 % Fe doped CuO_2, d) 0.3 % Fe doped CuO_2.

Conclusion

Nanocrystalline CuO_2 was synthesized by sol gel citrate method. Further it was modified by doping 0.1%, 0.2% & 0.3% Fe. As synthesized modified and non-modified CuO_2 was characterized by X-Ray diffraction to determine its crystallite size& EIS is carried out to study conductivity variation with doping % Fe and with temperature.

From XRD it is found that initial doping 0.2 % Fe in CuO_2 leads to increase its crystallite size but on further doping 0.1 & 0.3 % of Fe the crystallite size decreases drastically.
Variation of conductivity is studied with temperature and doping % of Fe. From the graph it is observed that conductivity is changes with increasing temperature but regular change is observed only in CuO_2 doped with 2% & 3% doped Fe, and this samples also shows highest conductivity amongst all the samples.

89

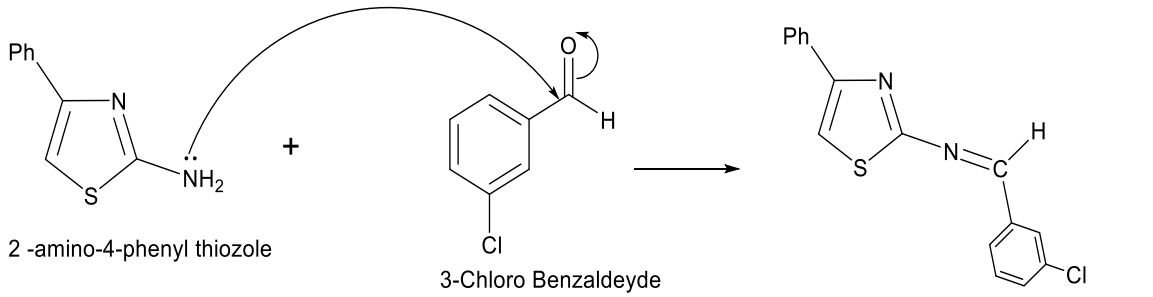
Synthesis, Characterization of (3-Chloro-benzylidene) – (4-Phenyl-thiazol-2-yl) amine and Studied their antioxidant Activity

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Abstract -
In the current study, substituted aromatic aldehydes (2a-c) were combined with 2- amino-4-phenyl thiazole to create a series of 4-phenyl-thiazolyl substituted Schiff bases (3a-c) derivatives. The IR and 1H-NMR of all the produced compounds validated their structures and its antibacterial activity was examined. All the title compounds were screened for their antibacterial activity. Most of the compounds exhibited moderate antimicrobial activity.
Keywords: Schiff's base; Aromatic Aldehydes; 3-Chloro-benzylidene) – (4-Phenyl-thiazol-2-yl) amine, Potassium ferricyanide.

Introduction-
In pharmaceutical chemistry, thiazole derivatives have been extremely important. Thiazole have a wide variety of pharmacological properties, including antimicrobial[1-4], analgesic[6-7], anticonvulsant[8-9], and antioxidant[10], hypolipidemic[11], anti HIV-1 [12-13], adenosine receptor antagonist[14-15] and osteoporosis inhibitor[16]. For the creation of antimalarial drugs, Schiff bases have proven to be intriguing moieties[17–18]. As potential antibacterial agents, Schiff bases have been mentioned[19–21]. It is imperative to find and create more powerful antifungal medicines, and several Schiff bases are well-known to be effective ones[22].

Reaction scheme



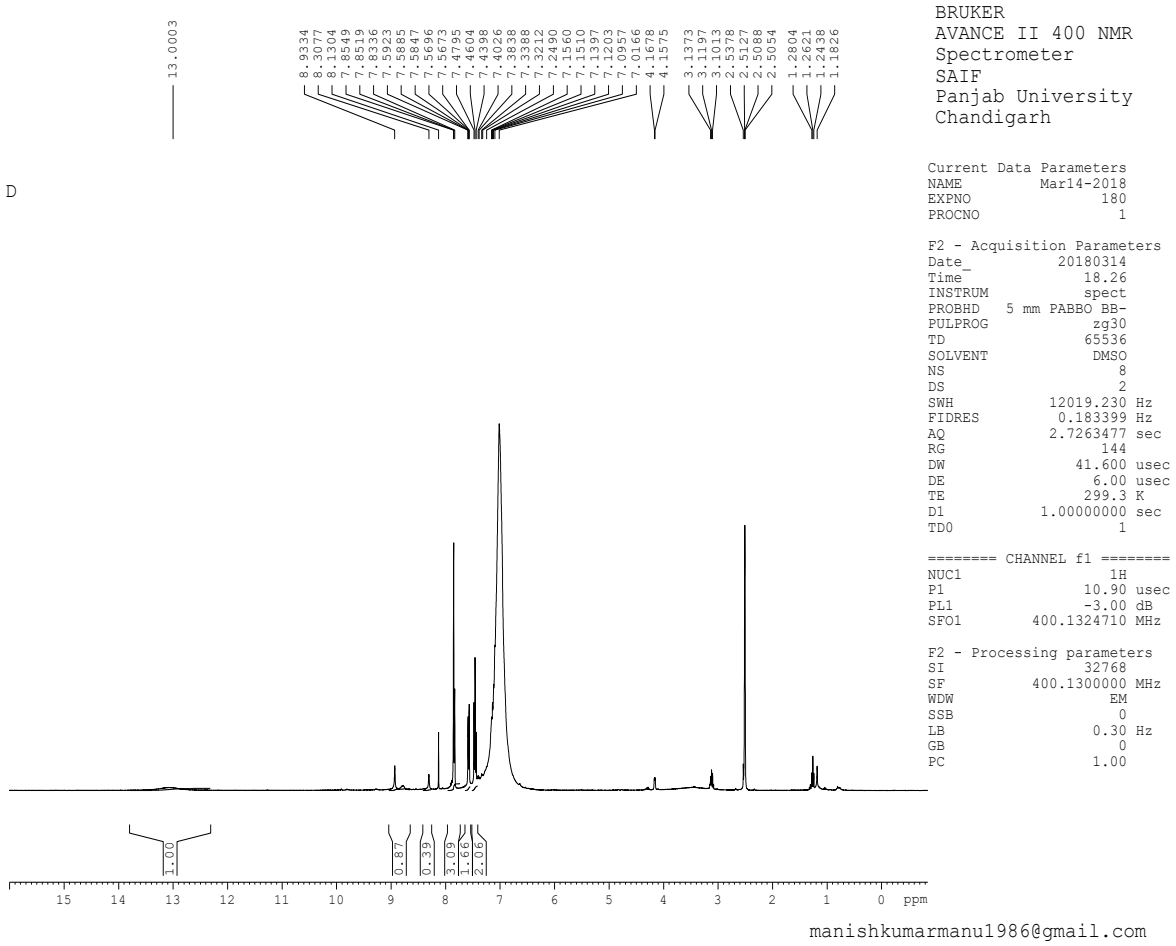
(3-Chloro-benzylidene)-(4-phenyl-thiazol-2-yl)-amine

Experimental Section
General Conditions: Melting points were discovered using open capillary tubes and are uncorrected. Iodine spotting and TLC were applied to the silica gel-G surface. Nicolet 5ZDXFT-IR spectrometers in the KBr phase and Brucker WP 200 and 500 SY spectrometers in the 1H NMR phase were used to record the IR spectra. Preparation of [(3-chloro-benzylidiene)-4-phenyl-thiazole-2-yl)-amine: general technique (3a) In the presence of HCl, (0.001mole) 2- amino 4- phenyl thiazole and 0.70gm of 3- chlorobenzaldehyde were refluxed for three to four hours. The product, M.P.-150-154^{0}C, was obtained from the resultant solid after it had been filtered, cleaned, and recrystallized from ethanol. 3a: 1HNMR: 2.6 (s,1H, CH3), 7.2-8.7 (m, 10H, Ar-H), IR (KBr): 1575 cm-1 (C=N)

IR Data

Sr. No.	Frequency in cm^{-1}	Assignment	Literature value cm^{-1}
1	3194.26	Ar -H	3300-2900
2	1608.70	C=N stretching	1640-1690
3	1473.68	C=C stretching	1400-1500

Antioxidant



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Ferric reducing antioxidant power assay

Reducing power assay method for determination of antioxidant activity/ potential of samples

Procedure:-

Different concentration of the drug (10-50ug/ml) was added to 2.5 ml of 0.2M sodium phosphate buffer (pH 6.6) & @.5ml of 1% potassium ferricynide [K3Fe(CN)6] solution. The reaction mixture was vortexed well & then incubated at 50^0 C for 20 min using vortex shaker. At the end of the incubation , 2.5 ml of 10% trichloacetic acid was added to the mixture and centrifuged at 3,000 rpm for 10min. The supermantant (2.5ml) was mixed with 2.5 ml of deionized water & 0.5ml of 0.1% ferric chloride. The coloured solution was red at 700nm against the blank with reference to standard using UV Spectrophotometer. Here, ascorbic acid was used as a reference standard.

The percentage of radical scavenging (%) was calculated by the following formula:

$$\% \text{ Free radical scavenging activity} = A_c - A_s / A_c \times 100$$

Where , A_c = Absorbance of control at 720 nm

A_s = Absorbance of sample

The concentration of sample required to scavenge 50% of the DPPH free radical (IC_{50}) was determined from the curve of percent inhibitions plotted against the respective concentration.

Experimental

Absorbance should increses with increses in concentration. Results confirm the reducing power Of samples which increased with increasing concentration. Higher value absorbance of the reaction mixture indicated greater reduing power. The redusing power was found to be on oreder Br>NO2.

Table 1 Ferric Reducing Antioxidant Power Assay

Standard Observation - (Ascorbic acid) (720nm)

Concentration(ug/ml)	Absorbance 1	Absorbance 2	Absorbance 3
10ug/ml	0.002	0.006	0.061
20ug/ml	0.395	0.251	0.029
30ug/ml	0.941	0.775	0.499
40ug/ml	1.451	1.350	1.036
50ug/ml	2.000	2.000	2.000

Control Absorbance - 0.812 (720nm)

Sample Observation- (720nm)

Formula –

$$\textbf{Scavenged(\%)} = (A_{cont}) - (A_{test}) / (A_{cont}) \times 100$$

Table2 (% Scavenged of DPPH free radical)

Sample name	Concentration	Absorbance	%Scavenged
4a (H)	g) 30ug/ml h) 50ug/ml	0.121 0.305	72.1 %
4b (OCH_3)	i) 30ug/ml j) 50ug/ml	0.213 0.504	68.2 %
4c (NO_2)	b) 30ug/ml 50ug/ml	0.068 0.463	62.9%
4d (Br)	k) 30ug/ml l) 50ug/ml	0.171 0.629	17.1%
4e (Cl)	b) 30ug/ml b) 50ug/ml	0.058 0.102	21.2%

Results and Discussion

Several five member aromatic systems having three hetero atoms at symmetrical position 1,3,4-thiadiazole had been studied because of their interesting physiological properties. Specifically substituted benzaldehyde or naphthaldehyde were combined with 2-amino-5-diethylamino-pentane in an equal amount of methanol to produce the desired Schiff-base phenols or Schiff base naphthalene ligands for evaluation [19]. Furthermore, by reducing their corresponding Schiff-base counterparts with KBH4 at 80°C for 3 hours, substituted amine phenol or amine naphthalene ligands were also produced [20].

All compounds underwent standard analytical procedure purification and characterization. The spectral and analytical data for digits 1 through 7 agreed with the suggested formulation. By measuring the incorporation of 3 H hypoxanthine, we assessed 1-7's capacity to prevent the formation of trophozoites in intraerythrocytic culture [21]. A more accurate way to quantify parasite development is through the inhibition of hypoxanthine incorporation, which correlates well with direct blood smear counts. Unfortunately, neither the CQ-sensitive (HB3) nor the CQ-resistant (Dd2) strains were significantly affected by compounds 1, 2, 3, 4, and 6. The

moderate half-maximal inhibitory concentration (IC50) values for the active compounds 5 and 7 against CQ-sensitive lines, respectively, were 5.53 and 6.38 M. However, compound 7 was found to be twice as effective as compound 5 against CQ-resistant Dd2 lines (IC50, 3.5 M for compound 5; 1.7 M for compound 7).

The structural differences of compounds 5 and 7 may be responsible for their varied biological actions. The quinoline ring of the CQ, which lacks chlorine at position 7 and the quinonyl basic nitrogen, has a simple substituted aromatic ring in position 5, but the quinoline ring of the 7 contains a naphthalene ring. Furthermore, it has been demonstrated previously that nitrogen atoms of side chain in chloroquine and aromatic ring assist in accumulation of the drug within the digestive vacuole of the parasite (Vydac) employing an eluent mixture of methanol and water (100% water for first 5 minutes, followed by a change to 50 : 50 (Water : MeOH) for the next 5-20 minutes, and finally 100% MeOH for the next 20-25 minutes). The retention times (Rt) are given for selected compounds.

Absorbance should increses with increses in concentration. Results confirm the reducing power Of samples which increased with increasing concentration. Higher value absorbance of the reaction mixture indicated greater reduing power. The redusing power was found to be on oreder Br>NO2.

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90

A Review: An Overview on Studies of Stability Constant of Metal Ions with Substituted Pyrazoles p^H-Metrically

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Abstract: This paper deals with review of stability constants of Metal ions and pyrazoles derivatives. The review is divided into two parts, a theoretical aspects and literature survey. In this paper, complexes of metal ions particularly transition metals & lanthanides are reviewed.

Keywords: Metal-ligand stability constant(logK), proton-ligand stability Constants(pK), pH metric titration and thermodynamic studies.

INTRODUCTION

In organic chemistry heterocycles having pyrazole ring plays an important role in life science along with pharmaceutical, medical, industriyal and agricultural science. The term Pyrazole was given by Ludwig Knorr in 1883. In 1959, the first natural pyrazole, 1- pyrazolyl-alanine was isolated from the seeds of watermelons. Coordination compounds play very important role in numerous chemical, biological and biochemical activities e.g. Chlorophyll, a magnesium complex essential for photosynthesis in plants; Haemoglobin, an iron complex, which carries oxygen to living organism cells; Coenzyme-Vitamin B12, a cobalt complex which serves as a prosthetic group in metabolic activities of living organisms. The study of enzyme has revealed that the site of reaction in biological systems is frequently a complexed metal ion. Coordination compounds have also played a very important role in biological activities for removal of undesirable and harmful metals from living organisms. The application of coordination chemistry is varied in the field of biological, biochemistry, medicine, agriculture, organometallic chemistry, solid state chemistry, catalysis and molecular receptors and devices. The metal ion complexes as a catalyst are invariably involved in various industrial processes. Stability constant is well known tool for solution chemist, biochemist, and chemist. In general to help for determination the properties of metal-ligand reactions in water and biological system [1]. In the study of coordination compound in solution, first and foremost requirement is the knowledge of stability constant of complex. For correct interpretation of complex, the knowledge of stability constant is essential. Reliable information of stability constant is of great importance in analytical and separation procedure. To remove undesirable and harmful metals from living organism, chelating agents are very much useful in biological systems. This gives importance to the study of determination of stability constant of metal complexes. The complexes have been extensively studied in solution as well as in solid state by many workers, due to it's remarkable properties and high stability. With the help of various experimental techniques, the extensive work in coordination complexes has been made possible and has lead in a number of empirical conclusions which have been detailed by Martell [2].

The stability of complex in solutions is depending on nature of central metal ion and ligands. The most important characteristics of the central atom which influence the stability of complex compounds are the degree of oxidation, the radius and electronic structure. Stability is dependent on the same characteristic in the ligand as considered for the cation in the case of complexes with monoatomic ligands. The strength of binding of ligand to the central metal ion

is depending on structure of ligand molecule or ions [3- 4]. The stability of complexes is dependent upon the size and number of chelating rings also. The structure of chelating agent determines the size of the chelating rings and the number of rings formed on chelation. Ley has concluded that five and six member rings of amino acid chelates are the most stable [5]. Pfeiffer has observed that, in general the five member ring is more stable when the ring is entirely saturated. But when one or more double bonds are present, the six member ring is favoured [6]. Schwarzenbach *et al* have observed that there is a decrease in chelate stability with the increase in ring size [7]. Tihile have observed increase in the value of formation constant with the presence of electron donating group [8]. S.V. Thakur have studied the stability of complex with changing temperature [9]. Irving and Williams give the stability order of metal complex of transition metal ion as Mn2+<Fe2+<Ni2+Zn2+ [10]. Though vast amount of work has been done on stability constant of metal complexes. Many workers study the effect of transition metal on a stability of complex by pH metrically [11-13]. Also there is a investigation of stability constant of ligand with lanthanide metals[14-17].The stability of metal complexes with medicinal drugs perform greater role in the biological and chemical activity [18].

pH-metry has been effectively adopted for the determination of stability constant J. Bjerrum and Ido-Laden's work enlightened the interest in the investigation of equilibrium of metal-chelates and ionic complexes in solution. Schwarzenbach and Ackermann (Schwarzenbach and Ackemann, 1948) found that stability of the chelates decreases as the increase of size ring. Complex or coordination compound and any substance, which can accept a pair of electron is calledas Lewis acid whereas any substance donating a pair of electrons is commonly called as Lewis base. When aligand contains two or more donor atoms close to each other, the metal complex formed is said to be a chelate and the process is referred as chelating. The chelating ring may be ionic or covalent depending on the nature of ligands. The history of complexes and the interpretation of complexes begin with Alfred Werner. Coordinating agents are used in metal-ion sequestration or removal, solvent extraction, dyeing, leather tanning, electroplating, catalysis, water softening, and in other industrial processes. For example, vitamin B_{12} is a coordination compound of cobalt, the heamoglobin of human blood is a coordination compound of iron, the haemocyanin of invertebrate animal blood is a coordination compound of copper, andthe chlorophyll of green plants is a coordination compound of magnesium.

Importance of stability constants

The stability constant of complexes has been found to be greater than zero, which is perhaps one ofthe most convincing pieces of evidence for the existence of the complex species ML_n in solution. Moreover, if all the possible stability constants for a given system have been determined, it is possible, in principle, tocalculate the equilibrium concentration or activity of each of the species present under a known set of experimental conditions. Such exact knowledge of the composition of a solution is essential for a correct interpretation of its optical and kinetic properties of partition equilibria and its biological behavior.

Factors affecting the stability of metal complexes

There are many factors, which assist the formation of a complex and sometimes hidden factors are working against the same. The capacity of a metal ion to form a complex with a ligand is mainly decided byits environment, which decides the stability of the complex. Some of the factors, which affect the stability of the complexes are solvents, tempreture, effect of metal ions, nature of ligands etc.

Determination of stability constant of binary complexes

The stability constant of complex in the solution is usually determined by the knowledge of measurement of equilibrium constants (K) for complex forming reaction. The knowledge of stability constant is, therefore, of immense help to rationalize our

understanding of the behaviors of metal chelate inthe solution. Followig methodology use to detemine stability constant of metal-ligand complex ions.

Methodology

I) P^H metric Calvin-Bjerrum Titration Method
II) Krucks and Sarkar method
III) Irving Rossotti method
IV) Half integral method of calculation
V) Spectrophotometric Method
  i) Method of Isobestic Point
  ii) Job's Method
  iii) Viscosity β-coefficient Method.
Iv) Adiabatic Compressibility Method

Literature Review:

study the stability constant, so that, we developed the environmentally benign protocol for the synthesis of Schiff bases and determine the stability constant of these Schiff bases by the pH-metric method.

The synthesis and characterization of an unique tetradentate Schiff bases were presented in this report namely: 2- (4,5dihydro-1,5-diphynyl-1H-pyrazole-3-yl) phenol (HL1) and 2-(4,5dihydro-5-(4-methoxyphenyl)-1-phynyl-1H-pyrazole-3- yl) phenol (HL2) and their copper complexes. On the basis of elemental analysis, magnetic susceptibility, conductivity, electronic, IR, ESR spectral data and powder X-ray powder diffraction observations indicated that for investigated complexes have been proposed octahedral geometry. The stability constants were determined using the pH metric technique. At various temperatures, a series of titrations using standard NaOH solution were performed. a temperature of 25°C and 30 0C. On the basis of experimental results and analysis it is observed that the values of proton-ligand stability constants and metal-ligand stability constants were found to decrease with increase in temperature. The antimicrobial and antifungal activities of the studied ligands as well as their copper complexes were evaluated using the cup plate technique at various doses in DMSO solvent using the minimum inhibitory concentration (MIC) method. The research indicates that Cu(II) complexes have high microbial activity, whereas ligands (HL) and (HL2) have moderate activity. [19]

The current study aimed to use silver ion (Ag+) complexes with pyrazole based ligands for developing spectroscopic method of silver ion in its aqueous solution with high sensitivity and low detection limits. The stability and composition of the complexes of 1,3-bis (3-(2-pyridyl) pyrazol-1-ylmethyl) benzene (1,3-PPB) and 1,4-bis (3-(2-pyridyl) pyrazol-1-ylmethyl) benzene (1,4-PPB) with Ag (I) ion have been investigated applying the spectrophotometric method in mixed (1:1) solvent of ethanol and water. Various experimental parameters, which include pH, ionic strength, solvent composition, and time, have been studied. The stoichiometry and formation constant of each complex have been evaluated spectrophotometrically. Spectrophotometric results indicated the formation of 1:1 complexes with stability order of Ag-1,4-PPB > Ag-1,3-PPB. Molar absorptivity values of the complexes have also been determined and were found to be 5039 and 6320, for Ag-1,3-PPB and Ag-1,4-PPB, respectively. The sensitivities for Ag determination by complexation with 1,3-PPB and 1,4-PPB were evaluated and found to be 0.045 and 0.055 mg.l-1, respectively. The Ag-PPB complexes could be used for Ag+ determination in aqueous solutions with high sensitivity and low detection limits.[20]

The interactions of Cu(II), Ni(II) and Cd(III) metal ions with 3-(4-chloro-1-hydroxynapthalene-2-yl)-5-(5-substituted furan-2-yl), 4-5 dihydro pyrazole-1-carbothioamide and 3-(4-chloro-1-hydroxynapthalen-2-yl)-5-(5-substituted furan-2-yl) pyrazole-1-carbothioamide have been studied at 0.1 M ionic strength in 70 % Dioxane-water mixture by

Bjerrum method. The values of proton-ligand stability constant (pK) and metal-ligand stability constants (log k) were calculated and compared by using the data obtained. The effects of substituent were studied from estimated data. The pK & log k values were also used to study the effect of substituents.[21]

In this Present investigation is attempted to make a methodical elucidations of the complex formation of Cu (II)ions with the pyrazole derived from 3(4-nitrophenyl)-4-benzoyl 5(2-hydroxy-4-bromo-phenyl) pyrazole and 3(4-chlorophenyl)-4- benzoyl 5(2-hydroxy-4-nitro-phenyl) pyrazole. The stability constants of their complexes with Cu (II) ions, have been studied by using Irving-Rossotti method at constant temperature 300K and ionic strength 0.01 M [22]

I Refractive index is useful for qualitative analysis of substances because each substance has constant and unique refractive index that can be determined with great accuracy. Refractive index of Substituted 1-phenyl-3-aryl-1Hpyrazol-4-carboxylic acid derivatives are determined by using Abbe's refractometer. Refractive index and density, molar refraction (Rm) and polarizability constant (a) are calculated from data. To study the solute-solute, solute-solvent and solvent-solvent interaction in the system, calculated data is used [23]

Ultrasonic study of substituted pyrazole carboxylic acid derivatives in 80% DMF-water at 305K is done. The experimental data is used to calculate Ultrasonic velocity, density, adiabatic compressibility (βS), intermolecular free length (Lf) and specific acoustic impedance (Z). These acoustic parameters are used to explain the interaction taking place in the solutions. Keywords: substituted pyrazole carboxylic acid derivatives, acoustic parameters and interactions in solution[24]

The hydrogen-ion activity in water-based solutions, its acidity or alkalinity expressed as pH scientifically is measured on the pH meter. pH meter instrument is also used to find out stability of complexes through titrations. Stability constant is equilibrium constant for the formation of a complex in solution. It is a measure of the strength of the interaction between the reagents that come together to from the complex. The proposed study deals with the proton-ligand stability constant and metal-ligand stability constant of chlorosubstituted pyrazoles and isoxazoles by Calvin Bjerrum titration on pH meter. [25]

Density and viscometric measurements of Substituted 1-phenyl-3-aryl-1H-pyrazol-4-carboxylic acid derivatives in binary mixture of 70% DMF-water are performed. Jones-Dole empirical equation analyzed the obtained data .Thermodynamic parameters enthalpy change(ΔH) , entropy change (ΔS) and Gibbs free energy change(ΔG) is determined. The interactions between solute-solute, solute-solvent and solvent–solvent interactions are studied [26]

The stability constant of substituted 2pyrazole (P1) with Cu(II), Co(II), Ni(II), Mn(II) complexes using pH metric titratio technique in 90% DMF-water mixture at an ionic strength of 0.1M KNO3 were studied. The data obtained showed that Cu (II) has highest stability while Mn(II) has lowest stability.[27]

The proton-ligand stability constants and metal-ligand stability constants of Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) with 3-(((3-(2- hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazono)indolin-2- one has been investigated potentiometrically using pH metric technique in aqueous, ethanol-water (50% v/v) and dioxane-water (50% v/v) mixtures at different ionic strengths (0.1 M and 0.2 M) of NaClO4 and at 25 ± 1 oC temperature. Proton-ligand stability constants values fall in the range of 9.642 to 11.751 attributable to ionization of phenolic –OH. The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine log K and log β values [28]

The complex formation between Cu(II), Ni(II), Co(II) and Fe(III) Metal Ions And 2-Hydroxy-4-(4'-Aminophenyl)-6-(2'-Hydroxy-5'-Bromophenyl) Pyrimidine[H4AHBP](L1) and 2-Hydroxy-4-(4'-Chlorophenyl)-6-(2'-Hydroxy-5'-Bromophenyl)Pyrimidine[H4CHBP](L2)

have been studied at 0.1 M Ionic Strength(30±0.1) 0C in 70% Diox ane-water mixture by Bjerrum method as adopted by Calvin and Wilson. It is observed that Cu(II), Ni(II), Co(II) and Fe(III)Metal ions form 1:1 and 1:2 complexes with ligands (L1 & L2). The data obtained were used to estimate and compare the values of proton-ligand stability constant (pK) and metal-ligand stability cons [29]

The physical properties such as viscosity and metal-bonding stability constant in 70% DMSO-Water and refractive index and polarazibility constant in different concentration with pyrazoles and diketones at 300c. The results obtained of stability constant are in good agreement. Measurements of refractive index have been studied by Abbe's refractometer. Molar refractivity and polarazibility constants of ligands solution have been evaluated in the present investigation. It could be seen that molar refractivity and polarazibity constants are found to be decreased with increase in density of solution.The stability constants of metal-ligand complex formation of Co(II) and Ni(II) with pyrazoles and diketones have been studied using Irving Rassoti's Method and titration is done by using Calvin BjerrumMethod in an inert atmosphere at 0.1M ionic strength and temp.(300c± 0.10c) pH metrically [30] 29

Spectrophotometric investigation of Co(II), Ni(II) and Cr(III) and Fe(III) complexes with 3-(2- hydroxy-3-nitro-4-methylphenyl)5-phenylisoxazole (L1) , 3-(2-hydroxyl-4-methyl phenyl)-5-phenyl isoxazoline (L2), 1-phenyl-3-(2-hydroxy-3-bromo-4-methyl phenyl)-5-phenyl pyrazole (L3), showed 1:1 and 1:2 complex formation between the pH range of 3.0 to 6.0 studied by Job's variation method at 0.1M ionic strength and 30°C ±1°C spectrophotometrically. The conditional stability constants are determined for 1:1 complexes at pH 3.0 and molar refraction and polarizibility constant for L1, L2 & L3 at different percentage of dioxane have also been calculated.[31] 30

In this paper, study the stability constants of the complexes of chloro pyrazoles with some metal ions and see the effect of various ionic strengths on the stability constants. The interactions of Cu (II), Tb (III) and Nd (III) metal ions with ligand i.e. 3 – (4 – Chlorophenyl) – 4 – (2 – furanoyl) – 5 – (2 – hydroxy phenyl) – pyrazole at various ionic strengths in 70% dioxane-water medium have been investigated by Calvin-Bjerrum pH metric technique at 270C. The obtained data was used to study the correct mechanism of the complexation reaction and the obtained results were used to study the thermodynamic constant.[32] 31

The proton-ligand and metal-ligand stability constants of the complexes of Cu(II), Ni(II),Co(II) with 1-Benzothiazol-2-yl-3-(2-hydroxy phenyl)-5-(4-methoxy phenyl) pyrazoline (L1), 1-Benzothiazol-2-yl-3-(2-hydroxy phenyl)-5-phenyl pyrazoline (L2), 1-Benzothiazol-2-yl-3-(2-hydroxy phenyl)-5-(4-chloro phenyl) pyrazoline(L3), 1-Benzothiazol-2-yl-3-(2-hydroxy-5-methyl phenyl)-5-(4-methoxy phenyl) pyrazoline (L4), 1-Benzothiazol-2-yl-3-(2-hydroxy-5-methyl phenyl)-5-(4-chloro phenyl) pyrazoline(L5) and 1-Benzothiazol-2-yl-3-(2-hydroxy-5-methyl phenyl)-5-phenyl pyrazoline(L6) have been determined by pH-metric method in medium of 80% acetone-water mixture at 0.1M ionic strength and at (30± 0.1) 0C temperature.[33] 32

The formation of complexes of Schiff base of (5-hydroxy-3-methyl-1-(2,4-dinitrophenyl)-pyrazol-4- yl)(phenyl) methanone and 4-amino antipyrine with metal ions at constant ionic strength (μ = 0.1M) in 70% 1, 4 dioxane-water mixture was investigated at 303K by pH-metric titration. The values of proton-ligand stability constant (pK) and metal-ligand stability constant (logK) obtained from the data. It is observed that the metal ions form 1:1 and 1:2 complexes with Schiff base of (5-hydroxy-3-methyl-1-(2,4- dinitrophenyl)-pyrazol-4-yl) (phenyl)methanone and 4-amino antipyrine.[34] 33

The inclusion properties of 3-amino-5-mÈthypyrazole (pyrazole) toward the alkali, alkaline earth cations, some transition, heavy metals and some lanthanides have been investigated in acetonitrile and methanol, followed by UV Spectrophotometry Absorption and conductivity. Thus, the stoichiometries of complexes formed and their stability constants were determined

by digital processing of data. The results of liquid-liquid extraction show that the ligand extracted only a Cs + and Mg 2+ in the series of the picrate salts considered [35] 34

The proton-ligand dissociation constant of 4-(4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-ylideneamino)-phenol(L1)and 4-(4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-ylideneamino)-benzoic acid (L2) and metal-ligand stability con-stants of their complexes with metal ions (Mn2+, Co2+, Ni2+, and Cu2+) have been determined potentiometrically in 0.1 mol·dm^{-3} KCl and 10% (by volume) ethanol-water mixture and at 298, 308, and 318 K. The stability constants of the formed complexes increase in the order Mn2+, Co2+, Ni2+, and Cu2+. The effect of temperature was studied, and the corresponding thermodynamic parameters (ΔG, ΔH, and ΔS) were derived and discussed. The dissociation process is nonspontaneous, endothermic, and entropically unfavourable. The formation of the metal complexes has been found to be spontaneous, endothermic, and entropically favourable [36]

The stability constants of 1-phenyl-3-(2-hydroxy-4-methylphenyl)-5-methylpyrazole (PHMPMPz) and their complexes with Pr (III) and Sm (III) metal ions have been determined in 70% v/v dioxane-water media at different ionic strength (0.02, 0.04, 0.06, 0.08, 0.1) mol.dm-3 at 300.15K by pH metry method. The pK and logK values decrease with increase in ionic strength of medium, which indicated the opposite charges on reacting species. The values of stability constants for Sm (III) were greater than Pr (III) metal ion. The thermodynamic stability constants at zero ionic strength have also been determined.[37] 35

The stability constants of the complexes of chlorosubstituted pyrazoles and pyrazoline in 70 % (v/v) dioxane-water mixture have been determined by PH -Meter. The proton-ligand and metal-ligand stability constants of Cu(II),Ni(II),Co(II) and Nd(III) metal ions with 3-(2-hydroxy-3,5-dichlorophenyl)-4-anisoyl-5-(4'-methoxyphenyl)-1-phenylpyrazole(L_1),3-(2-hydroxy-3,5-dichlorophenyl)-4-anisoyl-5-(4'-methoxyphenyl)-1-phenylpyrazoline(L_2)and 4-(2-chlorophenyl)-3-(3-furanoyl-5-(2-hydroxyphenyl) pyrazole(L3) have been performed pH metric method at 0.1 M ionic strength at 27± 0.10C. The value of Log K_1 and Log K_2 were used to determined the stepwise and simultaneous complex formation and to verify the validity of Log K= a. pK + b relation.[38]

Some new 3,5-Diaryl-1-substituted pyrazoles have been synthesized by the action of isonicotinic acid and thio-semicarbazide on 3-iodo flavanones in pyridine medium. 3-iodo flavanones obtained from 2-hydroxy-3,5-dichloro chalcones and ICl in acetic acid. Structure of these compounds has been established by chemical and spectral analysis (NMR & IR). Purity of these heterocycles was checked by TLC. The interaction of Cu(II), Co(II) with 1-carboxamido-3-(2-hydroxy-3,5-dichloro pheyl)-5-(4-methoxy phenyl) pyrazole (L_1), 1-thiocarbaxomedo-3(2-hydroxy-3,5-dichloro pheyl)-5-(4-methoxy phenyl) pyrazole (L_2) have been carried out by employing Bjerrum -Calvin pH metric titration technique, at 27 o C in 70 % dioxane-water medium. The data obtained can be used for the determination of proton ligand formation numbers (η). From the formation curve, the proton-ligand stability constant pK values have been evaluated using half integral method. The metal ligand formation numbers (η) are estimated by using Irving Rossotti's expression.[39]

The proton-ligand stability constants of some biologically important new pyrazoles and formation constants of their complexes with Ni (II) were determined at 0.1 mol dm-3 ionic strength and at 303.15 K in different dielectric constant of dioxane-water mixture by potentiometric method. The Calvin-Bjerrum's pH-titration technique as used by Irving and Rossotti was used for determination of stability constants. The results enabled to study the electrostatic forces of attraction between metal ion and ligand with changes in dielectric constant of the medium.[40]

The stability constant of complexes of Cu (II) metal ion with 3- (4-Chlorophenyl)-4 -(2 -chlorophenyl benzoyl) -5- (2- hydroxy phenyl) – pyrazole -L3 and 3- (4 - Chlorophenyl) -4-

(2-furanoyl)-5-(2-hydroxy phenyl)- pyrazole -L4 by Isobestic point method at wavelength 525 nm and 500 nm respectively and Cu (II), Nd (III) and Tb (III) metal ions with 3- (2-Hydroxy-3, 5-dichlorophenyl) -4-anisoyl- 5- (4'- methoxy phenyl) -1- phenyl pyrazole -L1 , 3- (2-Hydroxy -3, 5 -dichlorophenyl)- 4 -anisoyl-5- (4 -methoxy phenyl)-1- phenyl- Δ^2- pyrazoline -L_2 and 3-(4-Chlorophenyl) -4- (2- chlorophenyl benzoyl)-5-(2-hydroxy phenyl)-pyrazole -L3 were determined by Job's method. The measurement of absorbance was done by spectrophotometer. The conditional stability constants (log K) were calculated from the equilibrium constant (K) which obtained from the measured absorbance. The log K values were used to study the confirmation of complex formation.[41]

The formation of complexes of Dy (III), Nd (III), Sm (III) and Tb (III) with 3-(2-hydroxyphenyl)-5- pyrazole (HPPPZOLE) and 1-phenyl-3-(2-hydroxyphenyl)-5-pyrazole (PHPPPZOLE) was studied spectrophotometerically at (298 ± 0.1) K and ionic strength μ = 0.1 mol.dm . The stability constants have been -3 investigated in a 70% dioxane-aqueous mixture by the Job's continuous variation method. The results obtained of stability constants are in good concordance the values obtained by the real stability constant by pH metric technique.[42]

The stability constants of the complexes of Cu (II), Co (II) and Ni (II) ions with 3-(3'-nitrophenyl)- 4-(4"-chlorobenzoyl)-5-(2-hydroxyphenyl) pyrazole (L1), 3-(4'-chlorophenyl)-4-(4"-chlorobenzoyl)-5-(2- hydroxyphenyl) pyrazole (L2), 3-(4'-methoxyphenyl)-4-benzoyl-5-(2-hydroxyphenyl) pyrazole (L3), 3- (4-bromophenyl)-4-furoyl-5-(2-hydroxyphenyl) pyrazole (L4) have been determined by the pH-metric method at 0.1M ionic strength at 28 ± 0.10 C in 70% dioxane-water mixture. The data obtained were used to estimate the values of proton-ligand (pK) and metal-ligand (logK) stability constants. It is observed that Cu (II), Co (II) and Ni (II) metal ions form 1:1 and 1:2 complexes with all the ligands [43]

The interaction of metal ions with pyrazoles and diketons gained much interest as these compounds have importance in antidiabetiec drugs. The physical properties such as viscosity and metabonding stability constant in 70% DMSO-Water and refractive index and polarazibility constant in different concentration with diketones at 300 c. The result obtained of stability constants are in good agreement. Mesurement of refractive index has also been studied by Abbe's refractometer. Molar refractivity and Polarazibility constants of ligands solution have been evaluated in the present investigation. It could be seen that Molar Refractivity and Polarazibity constants are found to be decreased with increase in density of solution. The stability constants of metal-ligand complex formation of Cu(II) with pyrazoles and diketones have been studied using Irving Rassoti's Method and titration is done by using Calvin Bjerrum Method in an inert atmosphere at 0.1M ionic strength and temp.(300 c± 0.10 c) PH metrically.[44]

The pKa values of N-heterocyclic compounds (substituted pyrazoles) in a 70% (v/v) dioxane–water mixture have been determined using pH-metric measurements. The stability constants of the complexes of Dy (III), Nd(III), Sm(III), and Tb(III) with 3-(2-hydroxyphenyl)-5-methylpyrazole, l-phenyl-3-(2-hydimyphenyl)-5-methylpyrazole3-(2-hydroxy-4-methylphenyl)-5methylpyrazole, and l-phenyl-3-(2-hydroxy-4-methylphenyl)-5-methylpyrazole have been determined by the pH-metric method at (300 ± 0.1) K. The effect of ionic strengths on the complexes of Sm3+ and Pr3+ ions with pyrazole has been investigated in the internal from 0.02 to 0.1 mol dm–3 (sodium perchlorate) in the pH range 2–3.[45]

The reaction of Pr(III) and Nd (III) metal ions with L1 : 3 (2' - chlorophenyl) - 4- benzoyl - 5 (2- hydroxy phenyl) pyrazole, L2: 3 (2' -chlorophencyl) - 4- pyridoyl -5 (2-hydroxy phenyl) pyrazole, L3 : 3 (2' - aminophenyl)- 4-pyridoyl - 5 (2- hydroxyl phenyl) pyrazole and L4 : 3 (4' -chlorophenyl) 4- Benzoyl - 5 (2-hydroxy-phyenyl) pyrazole, have been studied pH-metrically at 0.1M ionic strength at 28 ± 0.10C in 70% ethanol -water mixture. The data obtained were used to estimate the values of proton-ligand (pK) and metal-ligand (logK)

stability constants. It is observed that Pr(III) and Nd(III) metal ions formed 1:1 and 1:2 complexes with all the ligands [46]

The stability constant of some metal ions like Sr(II), Cd(II), Pb(II) and Zn(II) complexes with substituted 1-Carboxamido-3-(2-hydroxy-5-methylphenyl)-5-phenylpyrazole (ligand1) and 3-(2-hydroxy5-methylphenyl)-5-phenylisoxazole (ligand 2) have been investigated by pH metric technic at 1 x 10-3 M ionic strength and at 30 ± 0.10 C in 70% alcohol (methanol) water mixture. The Data obtained were used to compare and evaluate the values of proton-ligand stability constant (pK) and metal-ligand stability constant(log k), proton-ligand and metal-ligand stability constant have been determined by Bjerrum method, it is observed that Sr(II), Cd(II), Pb(II) and Zn(II) metal ions forms 1:1 and 1:2 complexes with both ligands. The ligands and their corresponding complexes were also screened for their antimicrobial activities [47]

The reaction of Fe(II) and Ni (II) metal ions with L1 : 3 (2'- chlorophenyl) - 4- benzoyl - 5 (2-hydroxy phenyl) pyrazole, L2: 3 (2'-chlorophenyl) - 4- pyridoyl - 5 (2-hydroxy phenyl) pyrazole , L3: 3 (2'-aminophenyl)- 4-pyridoyl - 5 (2- hydroxyl phenyl) pyrazole and L4: 3 (4'-chlorophenyl) -4-Benzoyl -5(2- hydroxy-phyenyl) pyrazole, at 0.1M ionic strength at 28 ± 0.10C in 70% ethanol -water mixture and 70% dioxane-water mixture have been studied pHmetrically. The data obtained were used to estimate the values of proton-ligand (pK) and metal-ligand (logK) stability constants in different solvents. It is observed that the pK and logK values in 70% dioxane-water mixture are greater than in 70% ethanol -water mixture. Fe(II) and Ni(II) metal ions formed 1:1 and 1:2 complexes with all the ligands in both solvent medium.[48]

Conclusion

The above mentions information about the study the interaction of transition and inner transition metal ion with ligand to study the proton-ligand and metal-ligand stability constants were determined by Calvin- Bjerrum pH titration techniques as modified by Irving and Rossitti. In this review, Study Metal Ligand Stability Constant by pH Metric Technique have been summarized from 1904-2023.

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91

Synthesis of (E)-3-(5-chloro-2-hydroxyphenyl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)prop-2-en-1-one And Their Oxazine and Thizine derivatives.

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Abstract:-

The Synthesis of chalcones and its derivative has wide scope in chemistry due to its Shows different Biological Activities. The Chalcone Structure contain two aromatic ring linked by an aliphatic three carbon chain having alpha beta unsaturated ketone with reactive ethylenic group.in claisen-schimdt condensation equimolar quantities of aromatic aldehyde (without alpha hydrogen) and aromatic ketone (with active –CH group) React in the presence of Condensing reagent.in the present work 5-chloro 2-Hydroxy benzaldehyde react with 1,4-Benzodioxane 6-yl methyl ketone in the presence of potassium hydroxide to form 5-chloro 2-Hydroxy chalcone. chalcone identification was done with the help of thin layer chromatography.the newly synthesized 5-chloro 2-hydroxy chalcone was further reacted with urea,thourea in the presence of KOH we obtain oxazine and thiazine derivative of 5-chloro 2-hydroxy chalcone and this hydroxy chalcone react with hydroxylamine hydrochloride and hydrazine hydrate in the presence of KOH and sodium acetate we obtain isoxazole and pyrazole derivative of 5 chloro 2-hydroxy chalcone. Derivatives are confirmed with the help of TLC.
Key Words :- derivative, hydroxy chalcone,Chloro,synthesis.

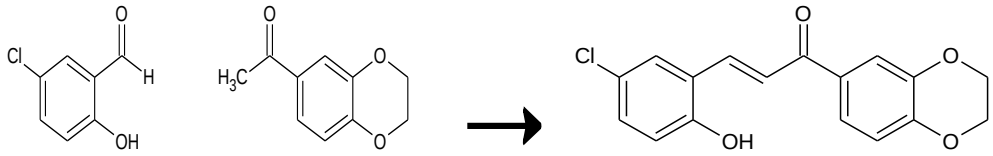
Introduction: Chalcones Synthesis process is a condensation process. The Clasen-Schmidt Condensation method also Applicable to synthesis of chalcones.in this process Aromatic Aldehyde react with Aromatic ketone in the presence of suitable condensing reagent to form chalcones.

Literature Survey reveal that Chalcones and its derivative,s are wide Application in Pharmacological Field it shows Various Biological activities in Various field. Different chalcone shows different pharmacological as well as different biological activities and its derivative also shows different biological and pharmacological activities. Due to wide range of application of chalcone and its derivative in the view that most interested topic is synthesis of chalcone and its derivative that's why synthesis of new chalcone and its oxazine derivative is important because it is new heterocyclic compound and it shows different biological as well as pharmacological Activities.

EXPERIMENT

Procedure for the synthesis of chalcones:

A mixture of 5-Chloro-2-hydroxybenzaldehyde (0.01 mol) and 1,4-benzodiaoxane-6-yl methyl ketone (0.01 mol) were dissolved in ethanol (25 ml) and 10% sodium hydroxide solution (25 ml) was added slowly and the mixture was stirred for near about 4 hrs. then it was poured in to 400 ml of water with constant stirring and left overnight in refrigerator. The precipitate as obtained after that it was filtered and re-crystallized with the ethanol.

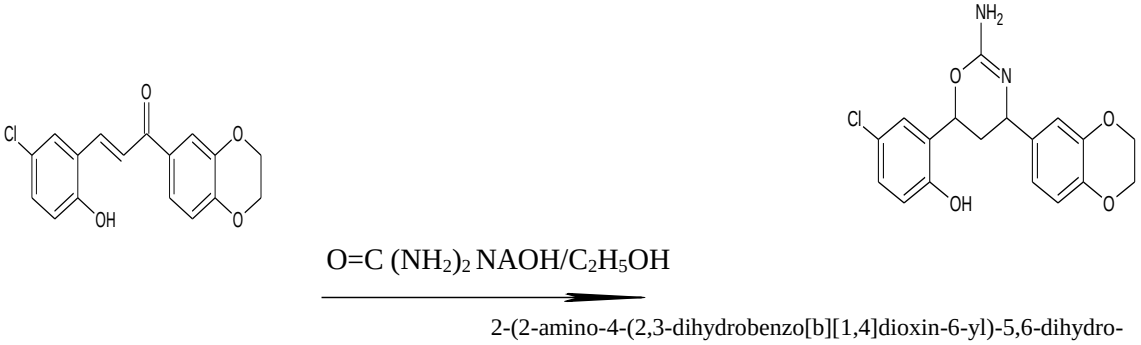


(E)-3-(5-chloro-2-hydroxyphenyl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)prop-2-en-1-one

Melting points of the compounds was determined in open capillary tubes and are uncorrected. Identification of chalcone compound with the help of thin layer chromatography was performed on TLC plate and spots were visualized by iodine vapor.

Preparation of chalcone derivative (oxazine derivative):

a mixture of 5-Chloro-2-hydroxy chalcone (0.02mol) and urea (0.02 mol) dissolved in ethanolic Sodium hydroxide solution (10 ml) was stirred for 2-3 hrs with magnetic stirrer it was poured in to 400 ml of cold water with continuous stirring for 1 hr then left overnight the precipitate was formed. Filtered the precipitate and washed it. After that re-crystallized the obtained product from ethanol. The completion of the reaction was monitored by TLCs.



2-(2-amino-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5,6-dihydro-4H-1,3-oxazin-6-yl)-4-chlorophenol

Preparation of chalcone derivative (thiazine derivative):

A mixture of 5-Chloro-2-hydroxy chalcone (0.02mol) and thiourea (0.02 mol) dissolved in ethanolic Sodium hydroxide solution (10 ml) was stirred for 2-3 hours with magnetic stirrer. It was poured in to 400 ml of cold water with continuous stirring for 1 hour and kept overnight. The precipitate was formed. It was filtered, washed and re-crystallized the product from ethanol. The



2-(2-amino-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6H-1,3-thiazin-6-yl)-4-chlorophenol

Result and Discussion:

The newly synthesized (E)-3-(5-chloro-2-hydroxyphenyl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)prop-2-en-1-one compounds were characterized by thin layer chromatography for the reacting 5-Chloro-2-hydroxybenzaldehyde (Rf value – 0.67) and for 1,4-benzodioxane-6-yl-methyl ketone (Rf value – 0.59) and the produced product (E)-3-(5-chloro-2-hydroxyphenyl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)prop-2-en-1-one (Rf value 0.75) were noted. This gives evidence for formation of the product. The product (E)-3-(5-chloro-2-hydroxyphenyl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)prop-2-en-1-one also showed the Wilson's test for chalcone. Melting point of concerning compound was detected in open capillary tube. The M.Pt.of (E)-3-(5-chloro-2-hydroxyphenyl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)prop-2-en-1-one was 184^0C.

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92

Structural Elucidation of Synthesized Substituted 1,3,4-Thiadiazole Molecules through Pharmacophore Modelling

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Abstract:
Heterocyclic compounds have found to be potent against microorganisms. Many heterocyclic molecules containing one or more heteroatom have been reported till date. Thiadiazoles are one of the biologically active heterocyclic compounds. Out of four isomers of thiadiazoles, 1,3,4-thiadiazole have reported to have better results. The synthesis of several 1,3,4-thiadiazole derivatives with increased antibacterial action is an ongoing endeavour. In this research article, prominent structural features of previously synthesised substituted 1,3,4-thiadiazole molecules are identified by studying their pharmacophore models comparatively. The comparative study of these 1,3,4-thiadiazoles resulted in variations in the hydrogen acceptor, hydrogen donor and lipophilic regions.

Keywords: 1,3,4-Thiadiazole, Pharmacophore Modeling, Antifungal, Antibacterial, Lipophilic, H-Bond Acceptor, H-Bond Donor

Introduction:

Heterocyclic compounds, characterized by the presence of at least one ring containing atoms other than carbon, such as nitrogen, sulphur, or oxygen, have emerged as a diverse and significant class of molecules with various biological activities. Among their many applications, heterocyclic compounds have gained considerable attention for their antimicrobial properties.[1-5] This note provides a comprehensive overview of the antimicrobial activities exhibited by various classes of heterocyclic compounds and their potential implications in the field of medicine. Thiadiazoles, a class of organic heterocyclic compounds containing a diazole ring with a sulphur atom, have garnered significant attention in recent years due to their diverse biological activities. Among these, the antimicrobial properties of thiadiazoles have been a subject of intense research. This note provides a concise overview of the antimicrobial activities exhibited by thiadiazoles and their potential implications in the field of medicine.[6-8] Thiadiazole exist in total four isomers which are 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5- thiadiazol and 1,3,4-thiadiazole. 1,3,4-thiadiazole derivatives are reported to have various pharmacological activities.

Malleshappa N. Noolvi, Harun M. Patel, Sarita Kamboj and Swaranjit Singh Cameotra in 2012 synthesised some novel 1,3,4-thiadiazole derivatives of 2-(4-formyl-2-methoxyphenoxy) acetic acid and evaluated theres *in vitro* antimicrobial activities against several microbial strains.[9] variations in the antimicrobial activities of these molecules are observed with variation in the type number and position of substituents. The present work is intent on development of pharmacophore models of these molecules. The pharmacophore models reveal hydrogen donor, hydrogen acceptor and lipophilic centres in the molecules. The structural variation in the molecules results in the variation in pharmacological activities of the molecules.

Experimental methodology:

a. Selection of database: [9]

The pharmacophore models of 19 previously synthesized molecules were developed using their database. The antibacterial activities of these molecules were screened against a bacterial strain 'S. enterica.' Almost all the molecules were found to be potent against S. enterica but some variations were observed. The % inhibitions values are mentioned in the table given below (Table:1). All the molecules are separated in some groups with similarity in the type, position and number of substituents and their % inhibition values were compared.

Table:1: Details of the molecules selected and their antibacterial activity against S. enterica

Sr. No.	Label	SMILES	% Inhibition
1	a	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4)C3)=C1	-
2	b	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4OC)C3)=C1	76.8
3	c	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(Cl)C=C4Cl)C3)=C1	85.0
4	d	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC(N)=C4)C3)=C1	68.6
5	e	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC([N+]([O-])=O)=C4)C3)=C1	93.2
6	f	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(OC)C=C4)C3)=C1	78.3
7	g	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(F)C=C4)C3)=C1	76.8
8	h	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C([N+]([O-])=O)C=C4)C3)=C1	97.0
9	i	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(Br)C=C4)C3)=C1	69.4
10	j	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(C)C=C4)C3)=C1	73.1
11	k	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC(O)=C4)C3)=C1	79.58
12	l	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4O)C3)=C1	73.8
13	m	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(Cl)C=C4)C3)=C1	79.1
14	n	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4N)C3)=C1	70.8
15	o	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(O)C=C4O)C3)=C1	76.8
16	p	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(N)C=C4)C3)=C1	86.5
17	q	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4Cl)C3)=C1	85.8

18	r	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(O)C=C4)C3)=C1	81.3
19	s	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC(C)=C4)C3)=C1	70.8

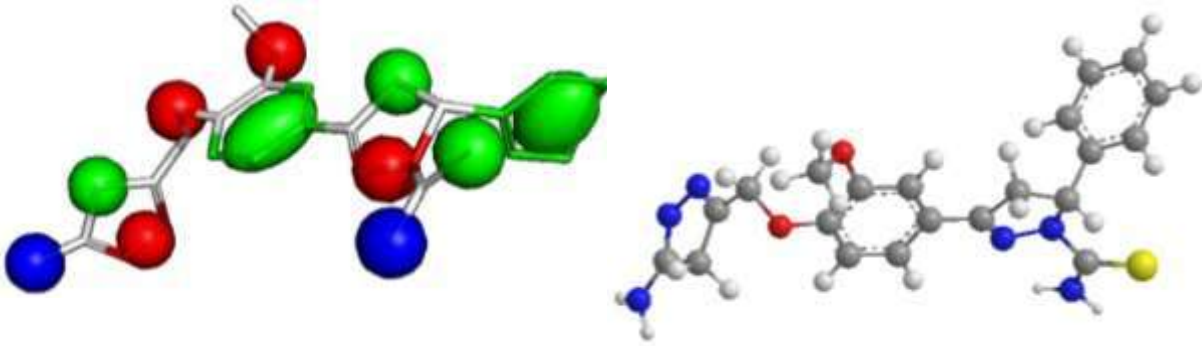
b. Development of pharmacophore model: [10-12]

Steps mentioned below are used for development of pharmacophore models.

a. Structure drawing: ChemSketch 12 freeware was used to draw structures of the molecules.
b. Structure optimization: Avogadro 2 was employed to optimize the 3D- structure.
c. Alignment of molecules: This step was accomplished using Open3Dalign.
d. Model generation: all the molecules were introduced in PyMOL 2.0. Then, PyMOL plugin 'LIQUID' was employed to generate consensus model using default settings.

Result and discussion:

All the molecules that are considered for comparative study of their pharmacophore models with respect to variation in the type and position of the substituents are divided into seven groups. Group I, II, IV, V and VI contains molecules which are positional isomers of each other. Pharmacophore based analysis of these molecules reveals the relation between their antibacterial activity against S. enterica and their H-bond donor, H-bond acceptor and lipophilic regions. All the molecules possess 5 lipophilic regions (green), 4 H-bond acceptor regions (red) and 2 H-bond donor regions in common as shown in the figure:1 given below. Variation in the substituents in the different molecules results in the variation in the number or size of H-bond acceptor, H-bond donor or lipophilic regions which eventually differentiate their antimicrobial activities. The details analysis of this is mention below.



Pharmacophore model of molecule-a 3D structure of molecule-a

Figure:1 Molecule-a

Table:2: Molecules divided in various groups

Sr. No.	Group	Label	Substitution	% Inhibition
1.	-	a	-H	-
2.	**I**	b	2-OCH_3	76.8
		f	4-OCH_3	78.3
3.	**II**	m	4-Cl	79.1
		q	2-Cl	85.8
4.	**IV**	n	2-NH_2	70.8
		d	3-NH_2	68.6
		p	4-NH_2	86.5
5.	**V**	e	3-NO_2	93.2

		h	4-NO_2	97.0
6.	**VI**	j	3-CH_3	73.1
		s	4-CH_3	70.8
7.	**VII**	l	2-OH	73.8
		k	3-OH	79.58
		r	4-OH	81.3

Group-I:

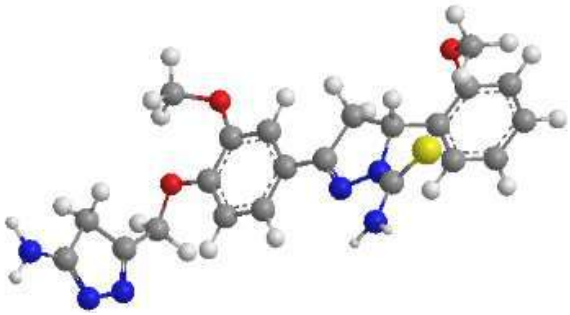


Fig 2: 3D structure of molecule-b

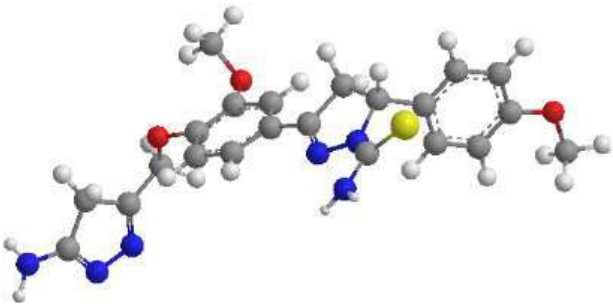


Fig 3: 3D structure of molecule-f

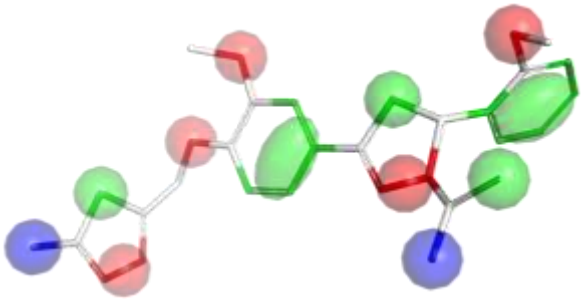


Fig 4: Pharmacophore model of molecule-b

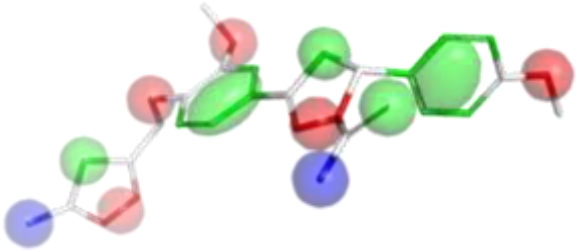


Fig 5: Pharmacophore model of molecule-f

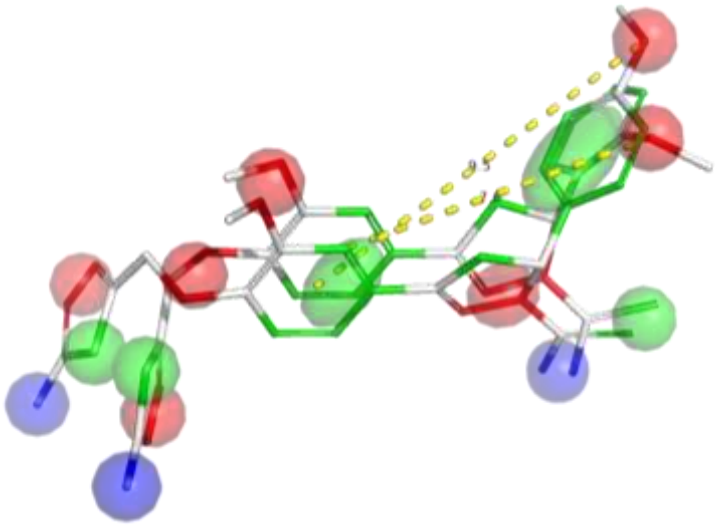


Fig 6: Consensus pharmacophore model of molecules b, and f represnting various regions (Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

Molecule b and f are positional isomers f each other. These molecules have almost similar potential against bacterial strain. The methoxy H-bond acceptor regions of methoxy groups are

responsible for increased antibacterial activity as compared to non-substituted ring. Though the distance between H-bond acceptor regions of methoxy groups and lipophilic region of central ring is not similar in both isomers but very small difference in their antibacterial activities is observed.

Group-II:

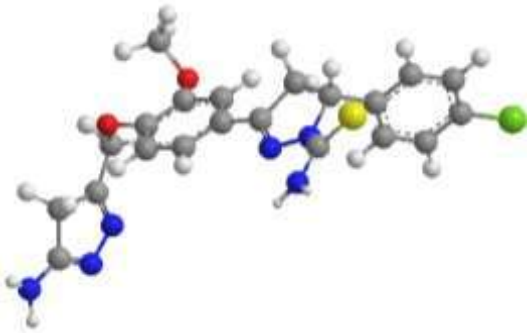


Fig 7: 3D structure of molecule-m

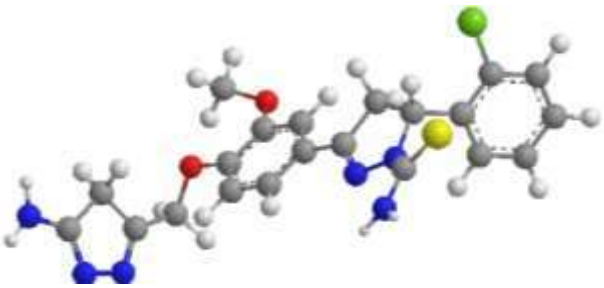


Fig 8: 3D structure of molecule-q

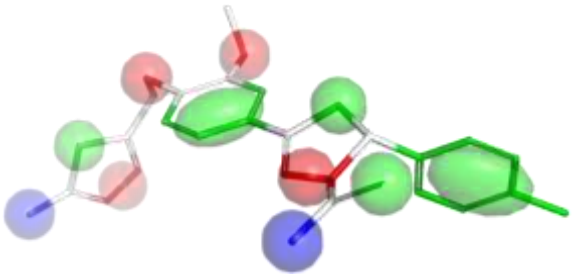


Fig 9: Pharmacophore model of molecule-m

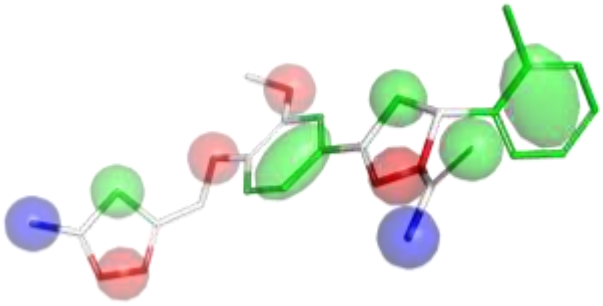


Fig 10: Pharmacophore model of molecule-q

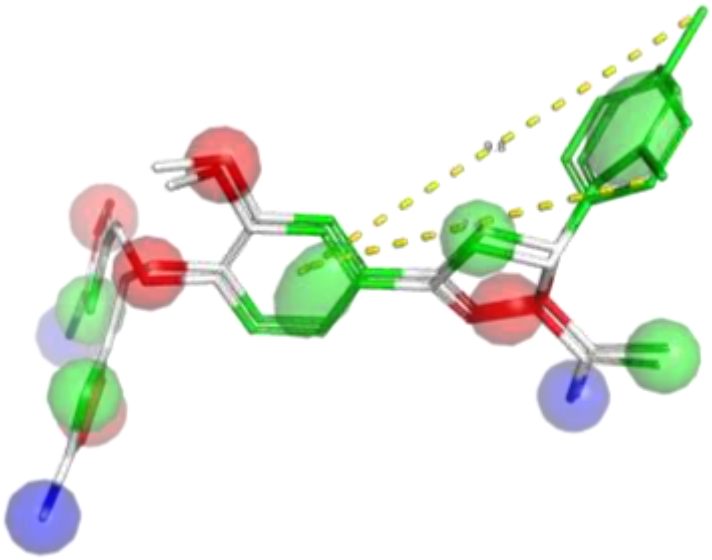


Fig 11: Consensus pharmacophore model of molecules m and q represnting various regions (Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

Positional isomers molecule m and q are due to change in the position of chlorine substituent. The increased lipophilic region of chlorine substituent is responsible for the increase in the antibacterial activity of molecule m and q. Much difference in the antibacterial activity of molecule m and q is observed. This might be because of the difference in the distance between central lipophilic region and lipophilic region of the chlorine substituents.

Group-III:

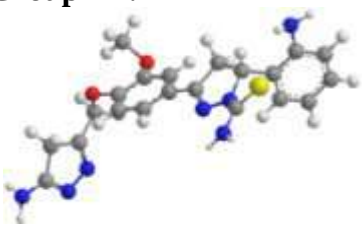


Fig 18: 3D structure of molecule-n

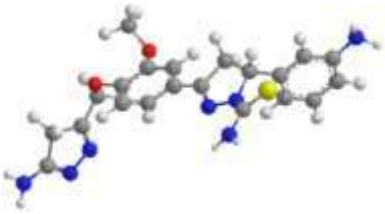


Fig 19: 3D structure of molecule-d

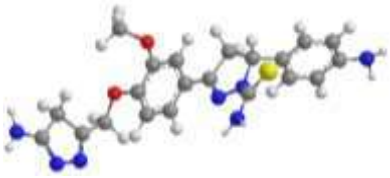


Fig 20: 3D structure of molecule-p



Fig 21: Pharmacophore model of molecule-n

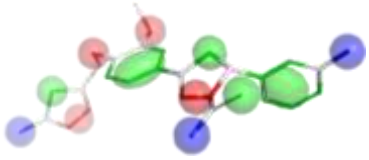


Fig 22: Pharmacophore model of molecule-d

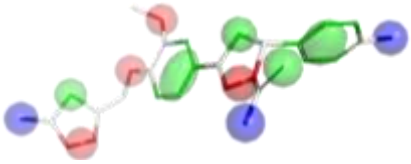


Fig 23: Pharmacophore model of molecule-p

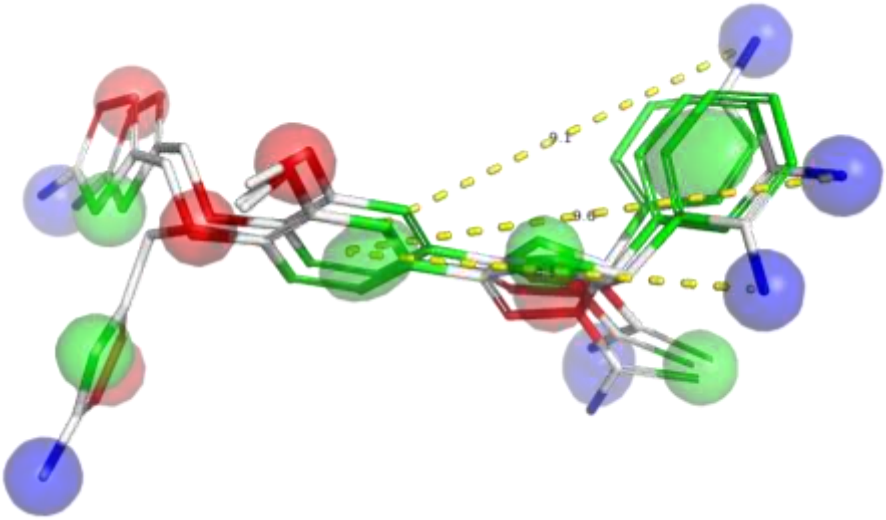


Fig 24: Consensus pharmacophore model of molecules n, d and p represnting various regions
(Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

Molecules n, d and are positional isomers of each other with variation in the position of amino group. The increased antibacterial activity of these molecules is due to the H-bond donor regions of amino substituents. Variation in the antibacterial activities of these molecules is observed with variation in the position of amino group. This variation is may be due to the difference in the distance between central lipophilic ring and H-bond donor amino groups. In the isomer with para-substituted amino group the distance is more and its antibacterial activity is also more as compared to ortho and meta isomers.

Group-IV:

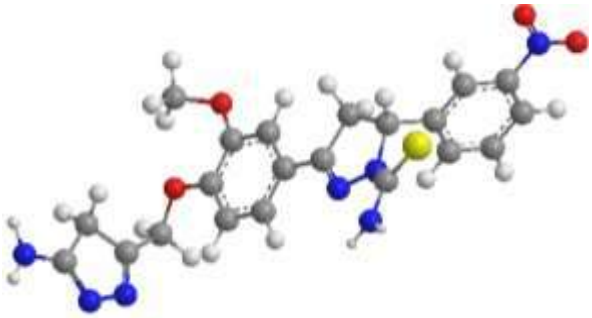


Fig 25: 3D structure of molecule-e

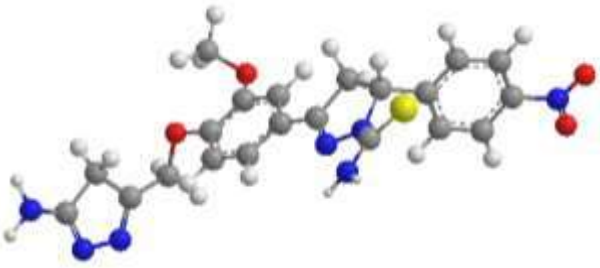


Fig 26: 3D structure of molecule-h

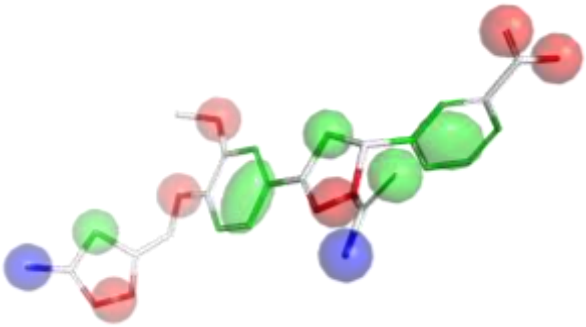


Fig 27: Pharmacophore model of molecule-e

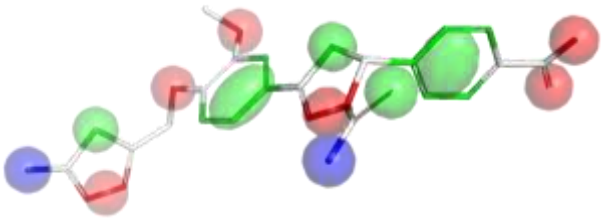


Fig 28: Pharmacophore model of molecule-h

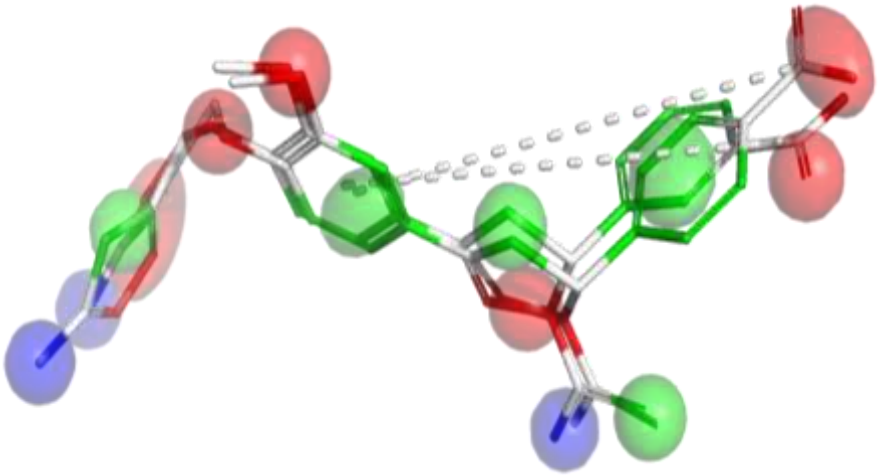


Fig 29: Consensus pharmacophore model of molecules e and h represnting various regions (Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

Molecules e and h are positional isomers each other with nitro group at meta position in molecule e and at para position in molecule h. The increased antibacterial activity of these molecules is due to the presence of H-bond acceptor region of nitro group. Both molecules have found to be most potent against bacterial strain amongst al the molecules examined. The para isomer is more potent as compared to the meta isomer due to increase in the distance

between H-bond acceptor region of nitro group at para position and central lipophilic region of ring.

Group-V:

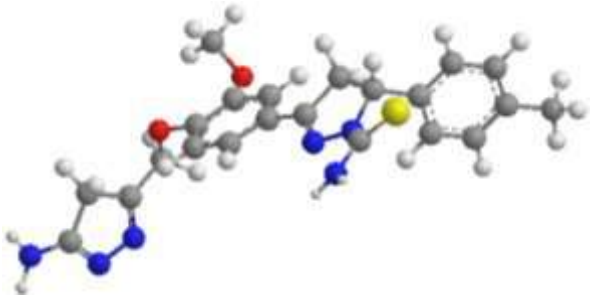


Fig 30: 3D structure of molecule-j

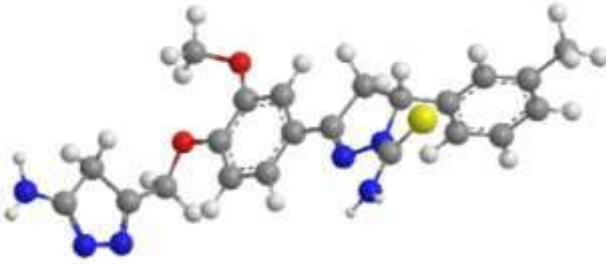


Fig 31: 3D structure of molecule-s

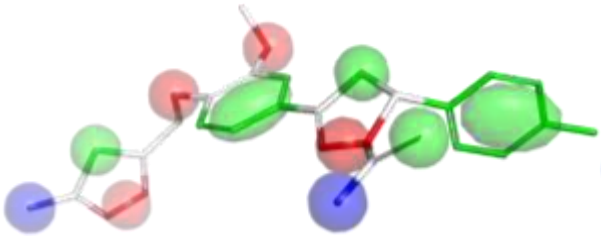


Fig 32: Pharmacophore model of molecule-j

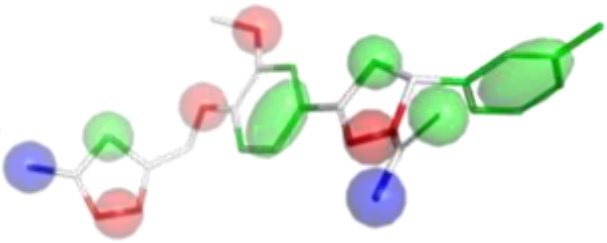


Fig 33: Pharmacophore model of molecule-s

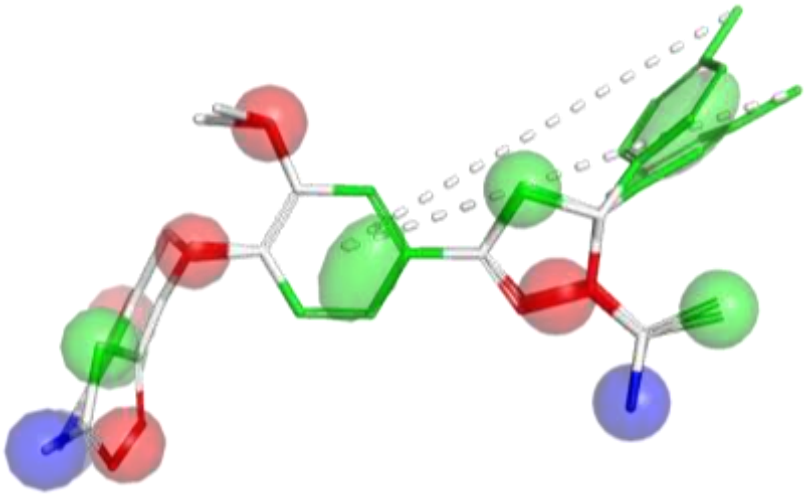


Fig 34: Consensus pharmacophore model of molecules j and s represnting various regions (Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

Molecules j and s are positional isomers of each other with methyl group at meta position in molecule j and at para position in molecule s. Increases in the antibacterial activity of these molecules is due to the increase in the lipophilic region of methyl group. Variation in the antibacterial activities of these molecules is observed with variation in the position of the methyl substituent. The para-methyl substituted isomer is found to be less potent as compared to the meta isomer due to increase in the distance between central lipophilic ring and lipophilic methyl substituent.

Group-VI:

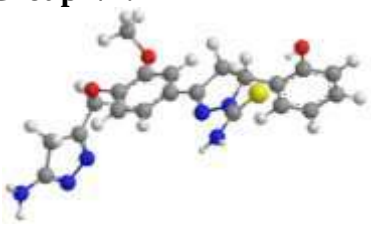


Fig 34: 3D structure of molecule-l

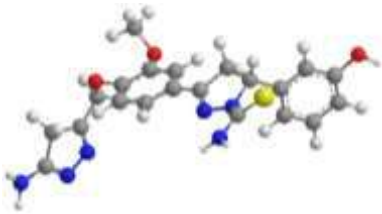


Fig 35: 3D structure of molecule-k

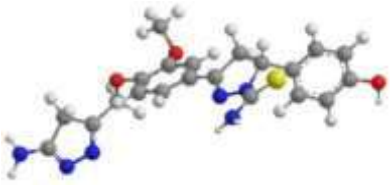


Fig 36: 3D structure of molecule-r



Fig 37: Pharmacophore model of molecule-l

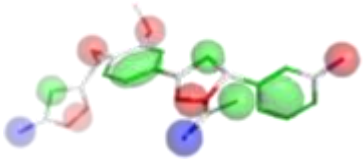


Fig 38: Pharmacophore model of molecule-k

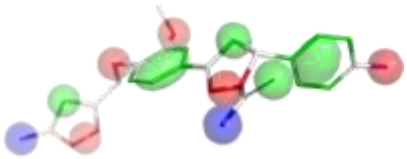


Fig 39: Pharmacophore model of molecule-r

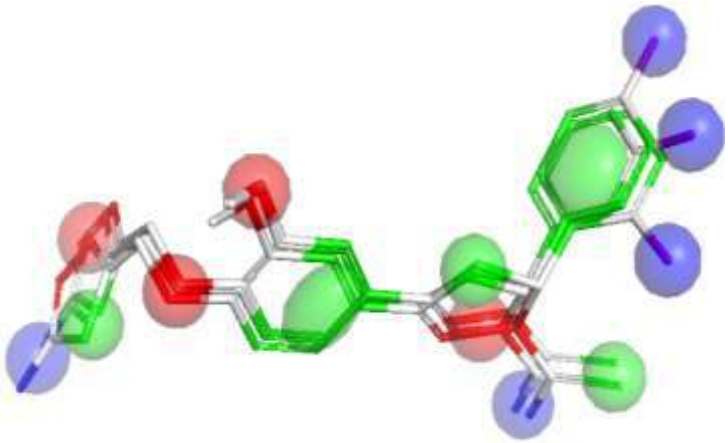


Fig 40: Consensus pharmacophore model of molecules l, k and r represnting various regions
(Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

Molecules l, k and r are positional isomers of each other with hydroxy substituent at ortho position in molecule l, at meta position in molecule k and at para position in molecule r. All these molecules have H-bond donor regions of hydroxy substituents at various positions which is responsible for their antibacterial activities. The variation in the antibacterial activity of these molecules is due to the variation in the position of hydroxy substituents. As distance between the central lipophilic ring and H-bond donor region of hydroxy groups increases in these positional isomers, the antibacterial activity increases.

A closer inspection of all molecules reveals that lipophilic, H-bond acceptor and H-bond donor regions of these molecules are responsible for their antibacterial activities. In group-I and group-II, H-bond donor region of methoxy and nitro group respectively are responsible for their antibacterial activities. Molecules with nitrogen substituents are most potent against bacterial strain amongst all the molecules studied. It is observed that in positional isomers with difference in the position of substituents responsible for H-bond donor regions, the antibacterial activity of these molecules increases with increase in the distance between the central lipophilic region of ring and the H-bond donor regions of methoxy or nitro substituents.

Molecules of group-II and group-V have chlorine and methyl substituents respectively that generates lipophilic regions which are responsible for their antibacterial activities. When the antibacterial activities of these molecules are studied, it is observed that distance between the central lipophilic region of the ring and lipophilic region of the substituents is inversely proportional to the potent of these molecules.

In case with molecules of group-III and group-VI, the amino and hydroxy substituents respectively are responsible for the H-bond donor regions. The potential of these molecules varies with position of the respective substituent. After observing the antibacterial activities of these molecules, it can be concluded that their potential increases with increases in the distance between the central lipophilic region of the ring and H-bond donor region of the amino or hydroxy substituent.

Conclusion:

The detailed study of the pharmacophore models of these molecules reveals that their antibacterial activity depends on the presence of the substituents responsible for lipophilic, H-bond acceptor and H-bond donor regions. The study also unveils that antibacterial potential of the positional isomers of these molecules depends on the distance between the central lipophilic region of ring the substituents, which is directly proportional for substituents responsible for H-bond acceptor and H-bond donor regions and inversely proportional for substituents responsible for lipophilic regions.

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93

Photocatalytic activity of Niobia-hematite Nanocomposites Synthesized by Sol-gel Method

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***Abstract*:**
In this investigation, Niobia-hematite (Nb_2O_5-α-Fe_2O_3) nanocomposites were synthesized by modified sol-gel method. The obtained materials were characterized by different techniques such as powder X-ray diffraction (XRD), field-emission scanning electron microscopy (FESEM), Brunauer-Emmett-Teller (BET), UV-vis diffuse reflectance (UV-vis spectroscopy). The catalyst was found to have a particle size in the region of 20-42 nm with a high surface area. The effects of the catalyst dose, the pH value, UV power, addition of H_2O_2 and scavenger on the photocatalytic efficiency were investigated. This study presents a strategy to eliminate highly toxic and persistent dyes such as DB 199 dye. It was observed that the nanocomposites showed maximum response with more than 80% degradation of DB 199 dye in 100 min.

Keywords: Nb_2O_5: α-Fe_2O_3: Nanocomposites: Photocatalysis: DB 199 dye:

1. Introduction

Owing to promising potential applications in battery cathode material, non-linear optics, Ionics, nanowires, photocatalysts and sensors, nanocomposites are of great interest in materials science [1]. For the past few decades, there has been considerable research in nanocomposites through the change in matrix phase and other geometrical variations helpful in applications enhancement of the materials. Hematite (α-Fe_2O_3), as a promising photocatalyst, has been widely investigated in photocatalytic degradation of organic contaminants [2]. It is the most stable state of iron oxides in ambient conditions and has the ability of efficient photodegradation and is able to harvest visible light up to 600 nm [3, 4]. Other salient features of hematite include its excellent stability, less toxicity, lower cost, inert behaviour and antiferromagnetic properties, also appeal its wide applications [5, 6]. The unfavourable defects of hematite structure, such as poor charge–transfer properties and faster recombination of charged species, are urged to be diminished. It was suggested that these structural and photochemical deficits can be possibly improved in multiple ways including morphological control, surface modification, synthesis of heterostructures and composites and/or doping with some other materials [7, 8]. Various previous studies indicated that coupling semiconductor metal oxides with hematite induces more active sites at the interface, which is favourable for photocatalysis [9-11]. Niobium pentoxide (Nb_2O_5), a typically nontoxic metal oxide, is eco-friendly and exhibits strong oxidation ability, and has attracted considerable attention from researchers. The applications of Nb_2O_5 based photocatalysts are reported in the photodegradation of plastics, reduction of CO_2, photocatalytic hydrogen evolution, and organic synthesis [12-16].

Dyes are widely used in many industries, such as the textile, rubber and cosmetics industries [17-20]. More than 10,000 types of dyes are suitable for industrial use and more than thousands of tons are produced in the world during the year [21]. Most of these dyes in nature not only create an unpleasant appearance but also weaken the penetration of light, reduce photosynthetic activity and inhibit biological growth. In addition, most of these dyes are toxic

and carcinogenic. The aim of the present investigation was to synthesize Niobia-hematite (Nb_2O_5-Fe_2O_3) nanocomposites by sol-gel method and study the photocatalytic degradation of Direct Blue 199 dye under the influence of UV and visible. The structure and surface physicochemical characterization of the synthesized materials were analyzed by X-ray diffraction (XRD) analysis, field-emission scanning electron microscopy (FESEM) and UV-visible spectroscopy. The effects of pH of the solution, photocatalyst dosage, effect of UV power, effect of H_2O_2 addition on the degradation efficiency were investigated.

2 Experimental

2.1 Synthesis of α-Fe_2O_3 nanoparticles

The method of synthesis of is mentioned in *Chapter IV* of the thesis. For the synthesis of α-Fe_2O_3 nanoparticles calculated quantity of $FeN_3O_9.9H_2O$ was mixed with 40 cc ethylene glycol and the mixture was stirred at 60˚C for 2 h. An aqueous solution of NH_3 was added under continuous stirring to give the corresponding pH in each synthesis. The reaction mixture was maintained at room temperature until a gel was formed; once the colloid was observed, it was kept for aging for 18 h which was dried in the oven at 80°C and then calcined in muffle furnace at 450°C for 4 h.

2.2 Synthesis of Niobia-hematite nanocomposites

For the synthesis of Nb_2O_5-α-Fe_2O_3 nanocomposites by sol-gel method, in a conical flask, 40 cc of niobium ethoxide was mixed with 90 cc of isopropanol and the solution was homogenized. In another flask, 15 cc of deionized water was mixed with the 25 cc ethanol-isopropanol (1:1) mixture and homogenized. Content of the second flask was added to the first flask. In order to reach the acidic pH of 4, hydrochloric acid was added dropwise to the mixture. Then calculated amount of α-Fe_2O_3 synthesized in the previous step was combined with the above solution and the mixture was placed on a magnetic stirrer for 2 hours. The obtained mass was then allowed to age for 18 h to obtained viscous gel. The resulting gel was dried in the oven at 100°C for 2 hours and obtained dry gel was heat-treated at 450°C and 500°C for 4 hours. The two nanocomposites obtained by heat treatment at 450°C and 500°C were referred as NF45 and NF50 respectively.

2.3 Characterization

As-synthesized samples were examined by X-ray diffraction (XRD) measurements on a Shimadzu X-ray diffractometer, equipped with Cu-Kα radiation source (λ = 0.154056 nm) at a scan rate of 5 min^{-1}. Bragg angle 2θ was ranged from 10 to 70°. Scanning electron micrographs were observed on a Zeiss Sigma Scanning Electron Microscope (SEM) operated at an acceleration voltage of 20 kV. The nitrogen adsorption/desorption isotherms at 77.35K were collected on an AUTOSORB iQ-MP instrument after heating the samples at 150°C for 2 h. The surface areas were estimated using the Brunauer-Emmett-Teller (BET) method.

2.4 Study of Photocatalytic Activity

The experimental set up used for photocatalytic degradation performance of Nb_2O_5-α-Fe_2O_3 nanocomposites is expressed in detail in *Chapter IV*. The photocatalytic test was carried out using a UV-photo reactor. Blue light fluorescent bulbs were positioned at the axis of the reactor to supply UV illumination. The reaction suspension was irradiated by UV light at a power of 18 W. In a typical photocatalytic degradation reaction, 10-40 mg/L of the catalyst powder was dispersed solution containing 50-200 ppm Direct Blue 199 dye and stirred for 1 h. Before starting the photocatalytic reaction, the reactor was kept in the dark and stirred for 30 min to ensure the adsorption/desorption equilibrium. During this time, dye molecules were adsorbed on the catalyst surface. Subsequently, the reactor was exposed to UV-light. At the interval of every 30 min, 5 mL aliquots were taken from the reaction mixture. The reaction mixture was then centrifuged, and the absorbance of the supernatant was measured by UV–Vis spectroscopy at the maximum absorption wavelength of the Direct Blue 199 dye (λ_{max} = 662 nm). The percentage of degradation efficiency was estimated by Equation (I);

$$\text{Degradation (\%)} = \frac{C_o - C}{C_o} \text{ x } 100 \quad (1)$$

where C_o and C denote the absorbance initially before exposure to UV-light and after exposure time t, respectively.

3. Result and discussion

3.1 X-ray diffraction

The purity and crystallinity of the as-prepared powder samples are measured by X-ray diffraction technique. XRD results reveal that the prepared α-Fe_2O_3 nanoparticles have a rhombohedral structure with the diffraction characteristic peaks are indexed as (012), (104), (110), (113), (024), (116), (018), (214), (300), and (220) planes corresponding to pure α-Fe_2O_3. The data were well corroborated with the literature data JCPDS card No. 84-0311 [22]. The presence of sharp, narrow, and highly intense peaks in the spectrum indicates the crystalline nature and purity of the synthesized α-Fe_2O_3 sample. The average crystallite size calculated from the most intense peaks using the Scherrer formula (Equation (II)). The average crystal size was found to be 27.4 nm.

$$D = \frac{0.9\lambda}{\beta cos\theta} \quad (2)$$

Where, D refers to the average crystallite size, λ is the wavelength of the *Cu Kα* X-ray radiation = 0.15406 nm, β refer to the full width at half maximum intensity of the peaks and θ and the Bragg angle, both measured in radians, respectively. XRD pattern of Nb_2O_5-α-Fe_2O_3 nanocomposites showed that the peaks observed belong to the α-Fe_2O_3 phases only. The reason for the absence of peaks related to Nb_2O_5 could be its low percentage in the nanocomposite and relatively lower calcination temperature employed in our experiment. From Figure 1, it can be seen that, at 450°C, intensity of peaks is smaller and increases strongly at 550°C.

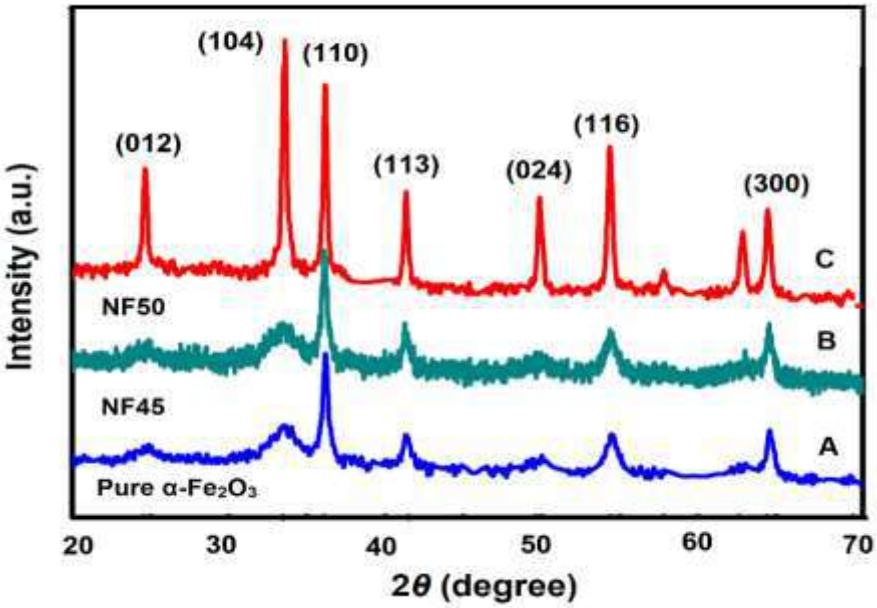


Figure 1 XRD pattern of pure α-Fe_2O_3 nanoparticles and Nb_2O_5-α-Fe_2O_3 nanocomposites.

3.2 Brunauer Emmet Teller (BET) surface area analysis

Specific surface area of as-prepared samples of nanocomposites was assessed using Brunauer Emmet Teller (BET) plot with relative pressure (p/p^o) ranging from 0.01 to 0.20. The sample calcined at the temperature 450°C has a specific surface area (NF45) of 207.35 m^2gm^{-1} as compared to the sample calcined at higher temperature of 500°C whose specific surface area (NF50) was 292.54 m^2gm^{-1}. It was concluded that the heat-treatment temperature has large effect on the surface area modification of Nb_2O_5-α-Fe_2O_3 nanocomposites.

3.3 UV-visible analysis

The UV-visible absorption spectrum of α-Fe_2O_3 and sample NF45 presented in Figure 2 shows three absorption bands at around 357, 539 and 672 nm. The absorption band present in the region of 400-600 nm can be assigned to d-d transition of Fe^{3+} as well as the pair excitations, 6A1 + 6A1 → 4T2 (4G) + 4T2 (4G) of two adjacent Fe^{3+} cations (6A1 and 4T2 (4G)), referred to as the ground state and first excited state configuration of high spin Fe^{3+}, respectively. Also, the band at 350 nm is mainly results from the ligand to metal charge-transfer transitions and partly from the contributions of the Fe^{3+} ligand-field transition 6A1 → 4T 2 (4D) [23]. The estimated band gap of the sample is found to be 2.03 eV for sample NF45 which is in good agreement with a band gap value of α-Fe_2O_3 [24]. The absorption edge in sample NF45 is indicative of the uniform particle morphology and size with fairly good crystallinity.

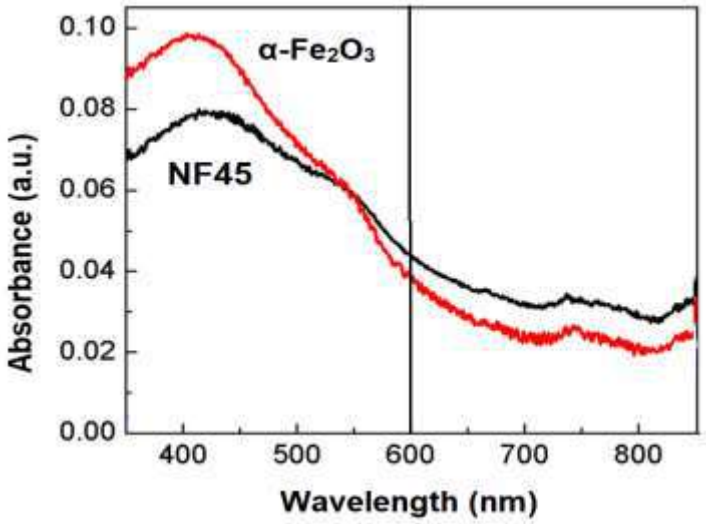


Figure 2. UV-visible absorption spectrum of pure and NF45 samples.

3.4 Photodegradation of direct blue 199 (DB) dye

3.4.1 Dark Reactions

The adsorption of dye was equilibrated onto the surface of as-prepared nanocomposites (figures are not shown) was studied initially. It was observed that regardless of the initial concentrations of the parent compounds, the steady state adsorption of dye was obtained after 50 min. The process was continued for 4 h and no significant reduction was observed.

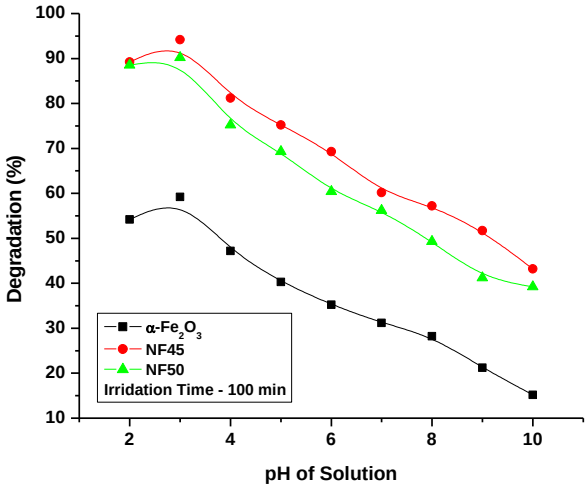


Figure 3. Effect of pH on photodegradation of DB 199 dye (100 ppm).

3.4.2 Effect of pH

The pH is an important parameter in the photocatalytic reactions taking place on the particulate surfaces as it dictates the surface charge properties of the photocatalyst. As reported earlier, the pH value has an influence on the kinetic of degradation of some organic compounds in photocatalytic processes [26-28]. In the present investigation, the degradation of DB dye (100 ppm) was studied at different pH values in the range 2 – 10 and the results are presented in Figure 3. The experimental results revealed that higher degradation of dye was found to be in strong acidic medium. The maximum degradation was observed at pH 3. This may be attributed to the electrostatic interactions between the positive catalyst surface and dye anions leading to strong adsorption of the latter on the metal oxide support. Moreover, the positive holes are considered as the major oxidation species formed at low pH which react with hydroxide ions forming hydroxyl radicals, thus the efficiency of process is enhanced. At increased pH, there is a columbic repulsion between negatively charged surface of catalyst and the hydroxide anions which prevent the formation of OH° and decrease the photocatalytic degradation [29].

3.4.3 Effect of catalyst loading

The effect of catalyst loading on the degradation of DB 199 dye was investigated using the varying concentration of as-prepared materials, keeping the other parameters identical. The results of this study are shown in Figure 4. One can see from Figure 5, that the maximum 99% degradation efficiency of DB 199 dye was observed for 20 mg/L of sample NF45 under UV-light within 100 min. A series of experiments were carried out by varying the catalyst amount from 10-40 mg/L in the aqueous solution of DB 199 dye. It can be seen that, initially the degradation efficiency increases with increase in amount of catalyst. With the catalyst dose 20 mg/L, the efficiency of dye degradation was found to be high and then efficiency decreased as the catalyst amount increased. This observation can be explained in terms of the number of active sites available for photocatalytic reactions. It was observed that large amount of catalyst may result in agglomeration of the catalyst molecules resulting in the decrease in the number of active sites [30, 31]. Another reason for decreased degradation efficiency can be attributed to increase in the turbidity of suspension due to excess of photocatalyst. This leads into the scattering of light resulting in the inhibition of photon absorption by the photocatalyst and hence the degradation efficiency.

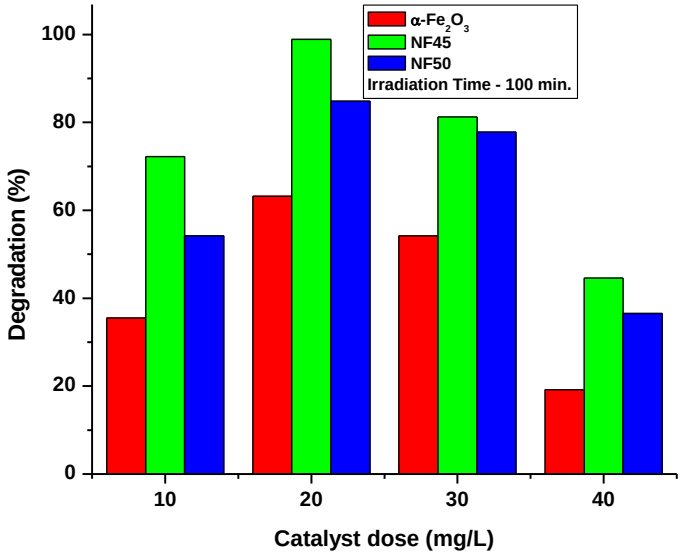


Figure 4. Effect of catalyst dose on photodegradation of DB 199 dye.

3.5.6 Stability test

In order to test the stability of the composite catalyst (20 mg/L), 10-times duplicate measurements were made with 100 min irradiation of DB 199 dye (100 ppm) at pH 3. The results are presented in Figure 5. From Figure 8, it can be observed that the degradation efficiency of NF45 nanocomposite after the 7–times reuse was similar to the first time and start declining afterwards with remarkable change.

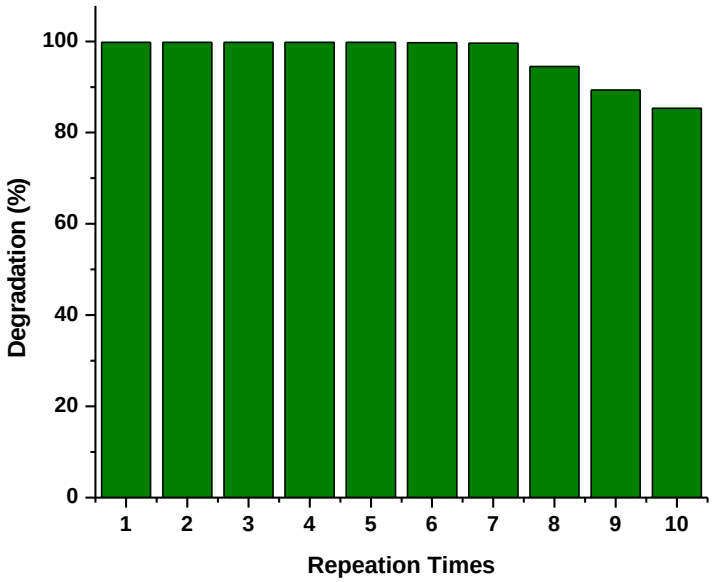


Figure 5. Experiment of repetitive use of NF45 nanocomposite.

4. Conclusion

In this study, Nb_2O_5-α-Fe_2O_3 nanocomposites were synthesized by modified sol-gel method and photodegradation analysis of Direct Blue-199 (DB 199) dye was done following various photo-catalytic pathways. The calcination temperature was optimized to be 450°C and 550°C. The nanocomposite calcined at 450°C, was found to be the efficient material for photodegradation of DB 199 dye due to its large surface area (207.35 m^2/g) and smaller crystallite size 12.58 nm. Addition of H_2O_2 increases the decolorization rate, as it enhances the generation of •OH. But beyond a limit it has negative impact on the reaction rate. In stability test, as-synthesized sample showed steady photocatalytic efficiency for more than five times. Future work may be extended for degradation of the textile effluents containing dyes as major pollutants.

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94

Pharmacophore Analysis of Substituted 1,3,4-Thiadiazole Derivatives: Unravelling Structural Insights for Enhanced Antibacterial Activity

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Abstract:
It has been discovered that heterocyclic compounds are effective against microbes. There have been several reports of heterocyclic compounds with one or more heteroatoms up to this point. Among the heterocyclic compounds with biological properties are thiadiazoles. From the four thiadiazole isomers, 1,3,4-thiadiazole has been seen to have superior performance. A number of 1,3,4-thiadiazole derivatives with stronger antibacterial activity are being synthesised. In this study, key structural characteristics of previously synthesised substituted 1,3,4-thiadiazole compounds are determined by comparative analysis of their pharmacophore models. These 1,3,4-thiadiazoles were compared, and the results showed differences in the lipophilic, hydrogen donor, and acceptor domains.

Keywords: 1,3,4-Thiadiazole, Pharmacophore Modeling, Antifungal, Antibacterial, Lipophilic, H-Bond Acceptor, H-Bond Donor

Introduction:

Heterocyclic compounds, which include at least one ring with an element other than carbon, such as oxygen, nitrogen, or sulfur—have become an important and diversified class of molecules with a range of biological activity. Heterocyclic compounds have several uses, but their antibacterial qualities have drawn a lot of interest.[1-5] This paper offers a thorough summary of the antibacterial properties displayed by several groups of heterocyclic compounds as well as any possible medical applications. Owing to their wide range of biological activities, thiadiazoles, a type of organic heterocyclic compounds having a diazole ring and a sulphur atom have attracted a lot of attention lately. Among them, thiadiazoles antibacterial qualities have been the focus of much study. This paper offers a succinct summary of the antibacterial properties of thiadiazoles and their possible medical applications.[6–8] There are four different isomers of thiadiazole in total: 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole. It has been observed that compounds of 1,3,4-thiadiazole exhibit a range of pharmacological properties.

In 2012, two new 1,3,4-thiadiazole derivatives of 2-(4-formyl-2-methoxyphenoxy) acetic acid were synthesised by Malleshappa N. Noolvi, Harun M. Patel, Sarita Kamboj, and Swaranjit Singh Cameotra. Their in vitro antibacterial properties were assessed against a variety of microbiological species.[9] Differences in the type number and position of the substituents are associated with fluctuations in the antibacterial activity of these compounds. The goal of the current effort is to construct pharmacophore models for these compounds. Hydrogen donor, acceptor, and lipophilic centres in the molecules are revealed by the pharmacophore models. The pharmacological actions of the molecules differ as a result of structural variations in the molecules.

Experimental methodology:

c. Selection of database: [9]

Their data was used to develop the pharmacophore models of 19 previously synthesised compounds. The bacterial strain *"M. smegmatics"* was used to test these compounds'

antibacterial properties. While significant variations were noted, almost all of the compounds were shown to be effective against S. enterica. The table below (Table:1) contains the percentage inhibitions values. All molecules are divided into groups based on similarities in the kind, location, and quantity of substituents, and the percentage of inhibition for each group was compared.

Table:1: Details of the molecules selected and their antibacterial activity against S. enterica

Sr. No.	Label	SMILES	% Inhibition
1	a	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4)C3)=C1	33.7
2	b	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4OC)C3)=C1	63.9
3	c	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(Cl)C=C4Cl)C3)=C1	-
4	d	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC(N)=C4)C3)=C1	58.1
5	e	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC([N+]([O-])=O)=C4)C3)=C1	75.5
6	f	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(OC)C=C4)C3)=C1	67.4
7	g	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(F)C=C4)C3)=C1	72.0
8	h	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C([N+]([O-])=O)C=C4)C3)=C1	81.3
9	i	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(Br)C=C4)C3)=C1	-
10	j	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(C)C=C4)C3)=C1	58.1
11	k	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC(O)=C4)C3)=C1	-
12	l	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4O)C3)=C1	-
13	m	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(Cl)C=C4)C3)=C1	80.2
14	n	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4N)C3)=C1	70.3
15	o	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(O)C=C4O)C3)=C1	79.6
16	p	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(N)C=C4)C3)=C1	83.1
17	q	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC=C4Cl)C3)=C1	74.4
18	r	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=C(O)C=C4)C3)=C1	65.6
19	s	COC1=C(OCC2=NN=C(N)C2)C=CC(C3=NN(C(N)=S)C(C4=CC=CC(C)=C4)C3)=C1	73.2

d. Development of pharmacophore model: [10-12]

Steps mentioned below are used for development of pharmacophore models.

e. Structure drawing: ChemSketch 12 freeware was used to draw structures of the molecules.
f. Structure optimization: Avogadro 2 was employed to optimize the 3D- structure.
g. Alignment of molecules: This step was accomplished using Open3Dalign.

h. Model generation: all the molecules were introduced in PyMOL 2.0. Then, PyMOL plugin 'LIQUID' was employed to generate consensus model using default settings.

i. Result and discussion:

Seven combinations comprise all of the molecules that are taken into consideration for a comparative analysis of their pharmacophore models regarding variations in the type and position of the substituents. Molecules in Groups I, II, IV and V are isomers of one another in terms of position. These compounds' antibacterial activity against M. smegmatis and their lipophilic, H-bond donor, and H-bond acceptor regions are related, according to pharmacophore-based study. As shown in the figure:1 below, all the molecules share 5 lipophilic areas (green), 4 H-bond acceptor regions (red), and 2 H-bond donor regions. Different molecules' substituent variations affect the quantity or dimensions of H-bond donors, acceptors, and lipophilic areas, which ultimately differentiate their antimicrobial activities. The details analysis of this is mention below.

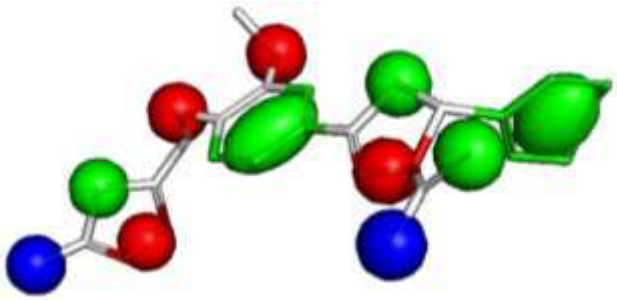
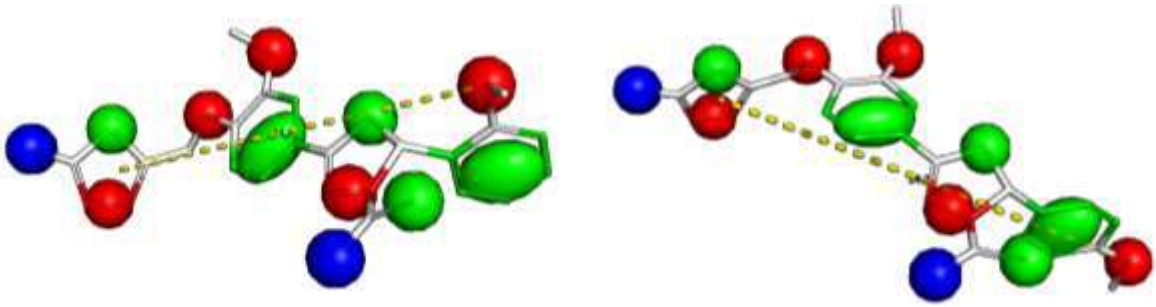


Figure:1 Pharmacophore model of molecule-a

Table:2: Molecules divided in various groups

Sr. No.	Group	Label	Substitution	% Inhibition
8.	-	a	-H	33.7
9.	**I**	b	2-OCH_3	63.9
		f	4-OCH_3	67.4
10.	**II**	m	4-Cl	80.2
		q	2-Cl	74.4
11.	**III**	n	2-NH_2	70.3
		d	3-NH_2	58.1
		p	4-NH_2	83.1
12.	**IV**	e	3-NO_2	75.5
		h	4-NO_2	81.3
13.	**V**	j	3-CH_3	58.1
		s	4-CH_3	73.2

Group-I:

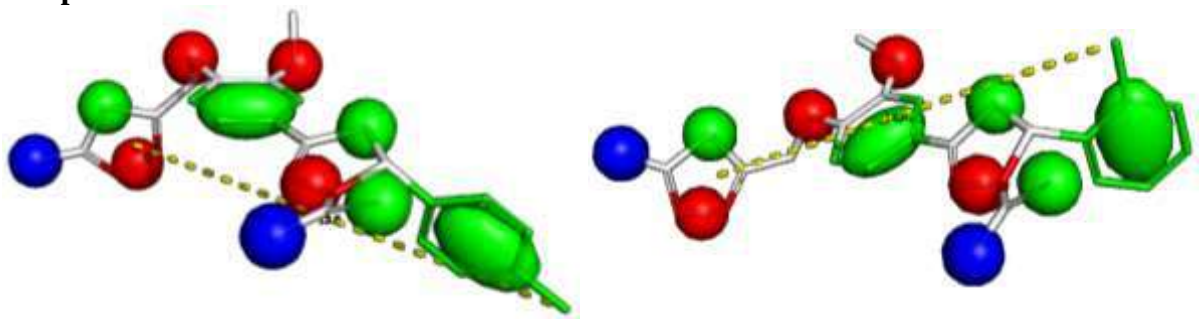


Molecule-b Molecule-f

Figure 2: Consensus pharmacophore model of molecules b, and f represnting various regions
(Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

The isomeric molecules b and f have increased antibacterial activity because of the H-bond acceptor region generated due to the presence of methoxy group. A difference in the antibacterial activity of the both the molecules is observed which due to the difference in distance between thiadiazole ring H-bond acceptor region of methoxy group. The antibacterial activity of the molecule f is more due to the increased distance.

Group-II:

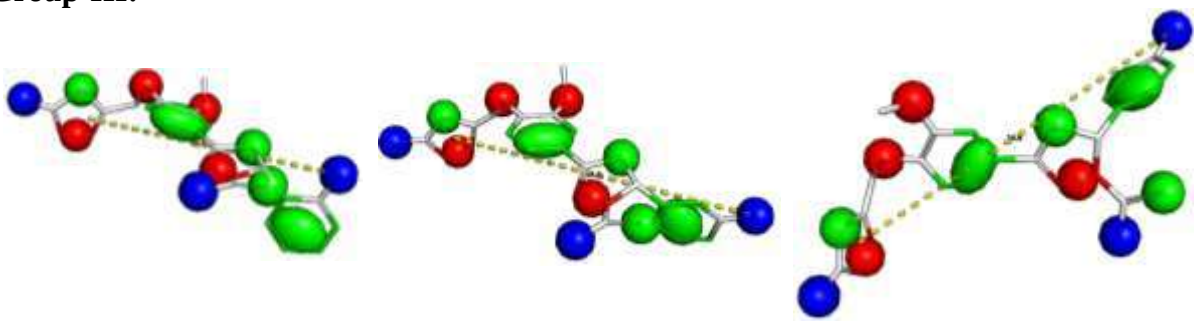


Molecule-m Molecule-q

Figure 3: Consensus pharmacophore model of molecules m and q represnting various regions
(Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

Molecules m and q are positional isomers of each other with variation in the position of methyl substituent which generates lipophilic region. The antibacterial strength of the molecules is different due to the difference in the distance between thiadiazole ring and lipophilic region of chlorine substituent. Molecule m is more potent as it has more distance between thiadiazole ring and lipophilic region of chlorine substituent.

Group-III:

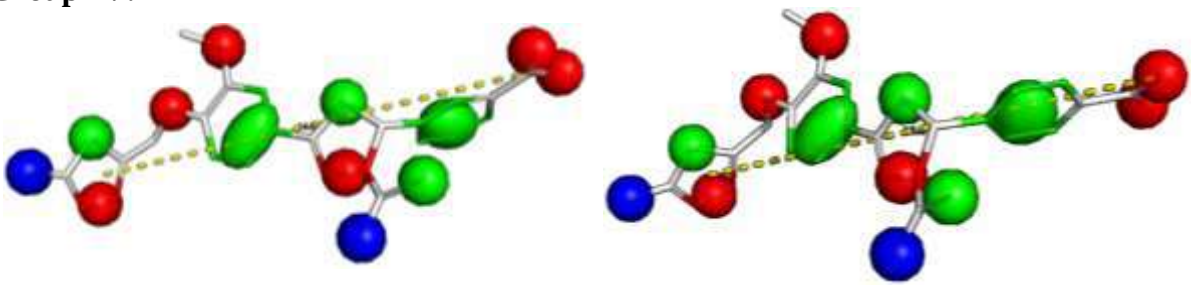


Molecule-n Molecule-d Molecule-p

Figure 4: Consensus pharmacophore model of molecules b, and f represnting various regions
(Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

The isomeric molecules n, d and p are more potent toward bacterial strain because of the H-bond donor region generated due to the presence of amino group. A difference in the antibacterial activity of these molecules is observed which due to the difference in distance between thiadiazole ring H-bond donor region of amino group. The antibacterial activity increases with increasing distance.

Group-IV:

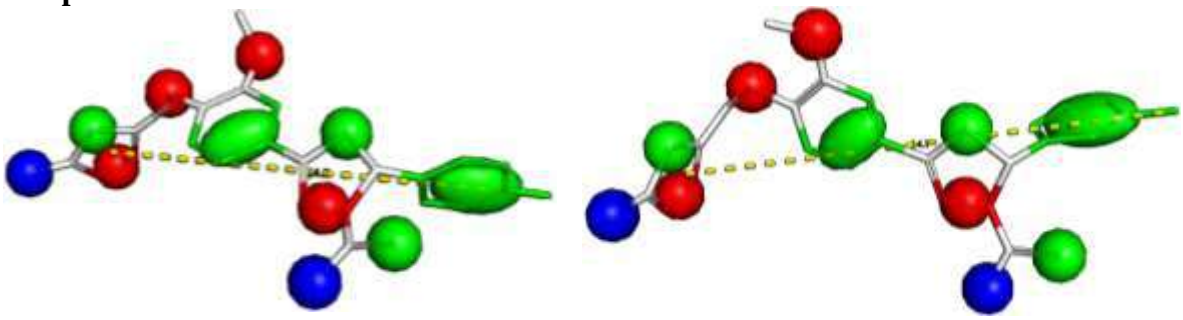


Molecule-e Molecule-h

Figure 5: Consensus pharmacophore model of molecules b, and f represnting various regions
(Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

Molecules e and h are positional isomers of each other with variation in the position of nitro group which generates H-bond acceptor region. The antibacterial strength of the molecules is different due to the difference in the distance between thiadiazole ring and H-bond acceptor region of chlorine substituent. Molecule h is more potent as it has more distance between thiadiazole ring and lipophilic region of chlorine substituent.

Group-V:



Molecule-j Molecule-s

Figure 6: Consensus pharmacophore model of molecules b, and f represnting various regions
(Green: Lipophillic, Red: H-Bond acceptor region, Blue:H-Bond Donor)

Molecules j and s are positional isomers of each other with variation in the position of chlorine substituent which generates lipophilic region. The antibacterial strength of the molecules is different due to the difference in the distance between thiadiazole ring and lipophilic region of chlorine substituent. Molecule s is more potent as it has more distance between thiadiazole ring and lipophilic region of chlorine substituent.

Upon further examination of each molecule, it becomes evident that the antibacterial properties of these compounds originate from their lipophilic, H-bond acceptor, and H-bond donor

regions. Of all the compounds examined, those having nitrogen substituents are the most effective against bacterial strains. The antibacterial activity of these molecules is found to change with an change in the distance between the thiadiazole ring and the H-bond donor regions, H-bond acceptor regions or lipophilic regions of the substituents.

Conclusion:

The detailed study of the pharmacophore models of these molecules reveals that their antibacterial activity depends on the presence of the substituents responsible for lipophilic, H-bond acceptor and H-bond donor regions. The study also unveils that antibacterial potential of the positional isomers of these molecules studied above depends on the distance between the central thiadiazole ring and the substituents.

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95

Exploring the Binding Affinity of N-Phenylbenzamide Derivative Using Pharmacophore Models in T. Brucei Parasites.

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Abstract:-
The current study investigated the T. Brucei inhibitory effect of substituted N-phenylbenzamide derivatives using consensus pharmacophoric analysis, a ligand-based drug design technique. Finding important elements that could be optimized in the future was the goal. The procedure includes structure drawing, optimization, file-based alignment, and the creation of pharmacophore models. The anti-T. Brucei activity requires aromatic rings as well as donor and acceptor groups of H bonds, the study claims. The findings might help refine N-phenylbenzamide derivatives for use as chagas disease preventive therapies.
Keywords: N-phenylbenzamide compounds, T. Brucei, anti-Chagas, and pharmacophore modelling.

Introduction

Three neglected tropical diseases caused by kinetoplastid parasites that cause immense suffering globally include Trypanosoma cruzi, Trypanosoma brucei, and Leishmania. Millions of people are at risk from leishmaniasis and the American and African trypanosomiases, mostly in the world's least developed countries [1–5].

Because they often target a specific stage of the illness or patient condition (e.g., late-stage rhodesiense sleeping sickness, chronic Chagas disease, and HIV/leishmaniasis coinfection), have poor efficacy against drug-resistant parasite strains, and require lengthy treatment regimens and high dosages with serious side effects, the current treatments for these conditions are ineffective[4-6]. Leishmania spp., T. brucei rhodesiense, and T. cruzi are zoonotic parasites that infect a range of domestic animals and further restrict treatment options. Therefore, new antiprotozoal drugs are needed to fortify this far from ideal therapeutic arsenal. Within the framework of the Medicines for Neglected Diseases a number of intriguing new chemical entities (NCE) are currently undergoing clinical development as part of the initiative (DNDi).

The polyadenylation specificity factor 3 (CPSF3) inhibitor acoziborole is a front-runner in phase I trials for leishmaniasis and Chagas disease, for instance, and its derivative DNDI-6148 has progressed to phase IIb/III for the single-dose oral therapy of gambiense human African trypanosomiasis (HAT). Recent research by Jonathan Nué-Martinez et al. [5] has revealed the effectiveness of N-phenylbenzamide derivatives as anti-Chagas agents. Owing to the extensive variety of substituents, the examined N-phenylbenzamide derivatives exhibit a high degree of anti-Chagas profile variability. Vast structure-activity relationships (SAR) analyses were conducted in order to identify significant scaffolds. This is the first attempt, therefore, to elucidate the pharmacophoric traits or pattern linked to the anti-Chagas action of modified N-phenylbenzamide derivatives. In order to understand the crucial structural properties that dictate the anti-Chagas effect of N-phenylbenzamide derivatives, consensus pharmacophore modeling was carried out in the current study.

2. MATERIALS AND METHODS

2.1. Dataset

The dataset contains 35 N-phenylbenzamide derivatives with a variety of substituents, such as heterocyclic rings, -CN, -OCH3, -Br, and various isomers. Therefore, a sizable portion of

chemical space is covered by the selected dataset. The compounds' anti-Chagas activity was assessed using T. Brucei of the wild type. The activity values that fall within the EC50 range are 0.12 to 85.6. The tabulated dataset is presented in Table 1.

Cmpd	SMILES	T. brucei, WT EC50 (nM)
3g	O=C(NC1=CC=C(NC(C2=NC=CC=C2)=N)C(Cl)=C1)C3=C(Cl)C=C(NC(C4=CC=CC=N4)=N)C=C3.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F	9.4 ₮ 0.96
2a	O=C(NC1=CC=C(/N=C2NC(C=CC=C3)=C3N\2)C=C1)C4=CC=C(/N=C5NC(C=CC=C6)=C6N\5)C=C4	85.6 ₮ 2.3
1i	O=C(NC1=C(F)C=C(/N=C2NCCN\2)C=C1)C3=CC=C(/N=C4NCCN\4)C(F)=C3.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F	78.5 ₮ 6.1
15	O=C(NC1=CC=C(/N=C2NC(C=CC=C3)=C3N/2)C=C1)NC4=CC=C(/N=C5NC(C=CC=C6)=C6N\5)C=C4	57.1 ₮ 1.4
1e	O=C(NC1=CC=C(/N=C2NCCN\2)C(Cl)=C1)C3=CC=C(/N=C4NCCN\4)C(Cl)=C3.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F	5.7 ₮ 0.7
2f	O=C(NC1=C(Cl)C=C(/N=C2NC(C=CC=C3)=C3N\2)C=C1)C4=C(Cl)C=C(/N=C5NC(C=CC=C6)=C6N\5)C=C4	5.56 ₮ 0.26
3h	N=C(C1=NC=CC=C1)NC2=CC(OC(C)C)=C(C(NC3=C(OC(C)C)C=C(NC(C4=NC=CC=C4)=N)C=C3)=O)C=C2.Cl.Cl	5.07 ₮ 0.03
1g	O=C(NC1=CC=C(/N=C2NCCN\2)C(Cl)=C1)C3=C(Cl)C=C(/N=C4NCCN\4)C=C3.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F	47.7 ₮ 13.2
1c	O=C(NC1=NC=C(/N=C2NCCN\2)C=C1)C3=NC=C(/N=C4NCCN\4)C=C3.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F	25.5 ₮ 3.2
3b	O=C(NC1=NC=C(NC(C2=NC=CC=C2)=N)C=C1)C3=CC=C(NC(C4=CC=CC=N4)=N)C=C3.Cl.Cl	23.7 ₮ 0.7
2g	ClC1=C(C(NC2=CC=C(/N=C3NC(C=CC=C4)=C4N\3)C(Cl)=C2)=O)C=CC(/N=C5NC(C=CC=C6)=C6N\5)=C1	2.64 ₮ 0.09
16	C1(/N=C2NC(C=CC=C3)=C3N\2)=CC=C4C(CC5=C4C=CC(/N=C6NC(C=CC=C7)=C7N/6)=C5)=C1	2.44 ₮ 0.18
14	C1(/N=C2NC(C=CC=C3)=C3N\2)=CC=C(CCC4=CC=C(/N=C5NC(C=CC=C6)=C6N\5)C=C4)C=C1	2.3 ₮ 0.2
1h	O=C(NC1=CC=C(/N=C2NCCN\2)C(OC(C)C)=C1)C3=C(OC(C)C)C=C(/N=C4NCCN\4)C=C3.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F	17.6 ₮ 2.1
3f	N=C(C1=NC=CC=C1)NC2=CC(Cl)=C(C(NC3=C(Cl)C=C(NC(C4=NC=CC=C4)=N)C=C3)=O)C=C2.Cl.Cl	15.5 ₮ 2.7
2c	O=C(NC1=NC=C(/N=C2NC(C=CC=C3)=C3N\2)C=C1)C4=NC=C(/N=C5NC(C=CC=C6)=C6N\5)C=C4	11.3 ₮ 0.2
3d	O=C(NC1=C(Cl)C=C(NC(C2=NC=CC=C2)=N)C=C1)C3=CC=C(NC(C4=CC=CC=N4)=N)C(Cl)=C3.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F	10.5 ₮ 1.9
1f	O=C(NC1=C(Cl)C=C(/N=C2NCCN\2)C=C1)C3=C(Cl)C=C(/N=C4NCCN\4)C=C3.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F	10.4 ₮ 0.8
2d	O=C(NC1=C(Cl)C=C(/N=C2NC(C=CC=C3)=C3N\2)C=C1)C4=CC=C(/N=C5NC(C=CC=C6)=C6N\5)C(Cl)=C4	1.96 ₮ 0.03
2e	O=C(NC1=CC=C(/N=C2NC(C=CC=C3)=C3N\2)C(Cl)=C1)C4=CC=C(/N=C5NC(C=CC=C6)=C6N\5)C(Cl)=C4	1.68 ₮ 0.06
3a	O=C(NC1=CC=C(NC(C2=NC=CC=C2)=N)C=C1)C3=CC=C(NC(C4=CC=CC=N4)=N)C=C3	0.40 ₮ 0.02
3e	O=C(NC1=CC=C(NC(C2=NC=CC=C2)=N)C(Cl)=C1)C3=CC=C(NC(C4=CC=CC=N4)=N)C(Cl)=C3.FC(F)(C(O)=O)F.FC(F)(C(O)=O)F	0.25 ₮ 0.04
3c	O=C(NC1=NC=C(NC(C2=NC=CC=C2)=N)C=C1)C3=NC=C(NC(C4=CC=CC=N4)=N)C=C3	0.12 ₮ 0.01
1a	O=C(NC1=CC=C(/N=C2NCCN\2)C=C1)C3=CC=C(/N=C4NCCN\4)C=C3.Cl.Cl	0.83

Note: not determined

2.2 Drawing, optimizing, and aligning structures

Using the free ChemSketch 12 tool, 35 structures were designed. Each structure was then optimized using the MMFF94 force field from TINKER. (3) The next step included aligning all of the ideal structures using the Open3dAlign program. (4) Consensus pharmacophore

modeling was carried out with the LIQUID plugin, installed on PyMOl 2.2, with default parameters [6–8].

3. RESULTS AND DISCUSSION

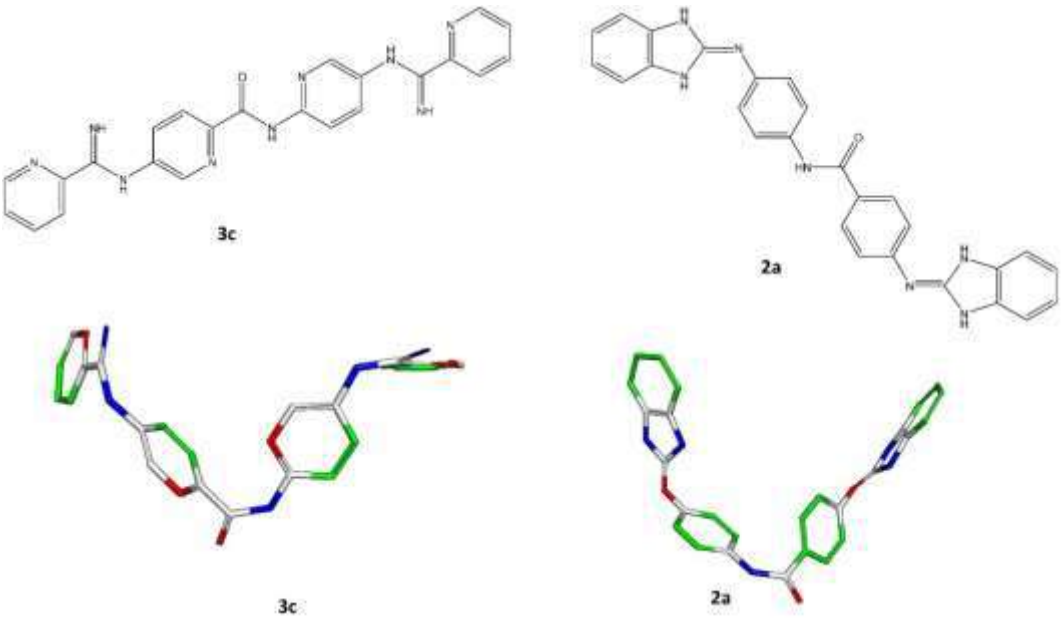


Figure 1: The two most active molecules, 3c and 2a, respectively, have 2D and 3D structures. According to the 2D structure, the 3c molecule has a U-shape, while the 2a molecule has a necklace-shaped N-phenylbenzamide ring connected with two Aminobenzimidazole rings. The 3c molecule also displays five pyridine rings.

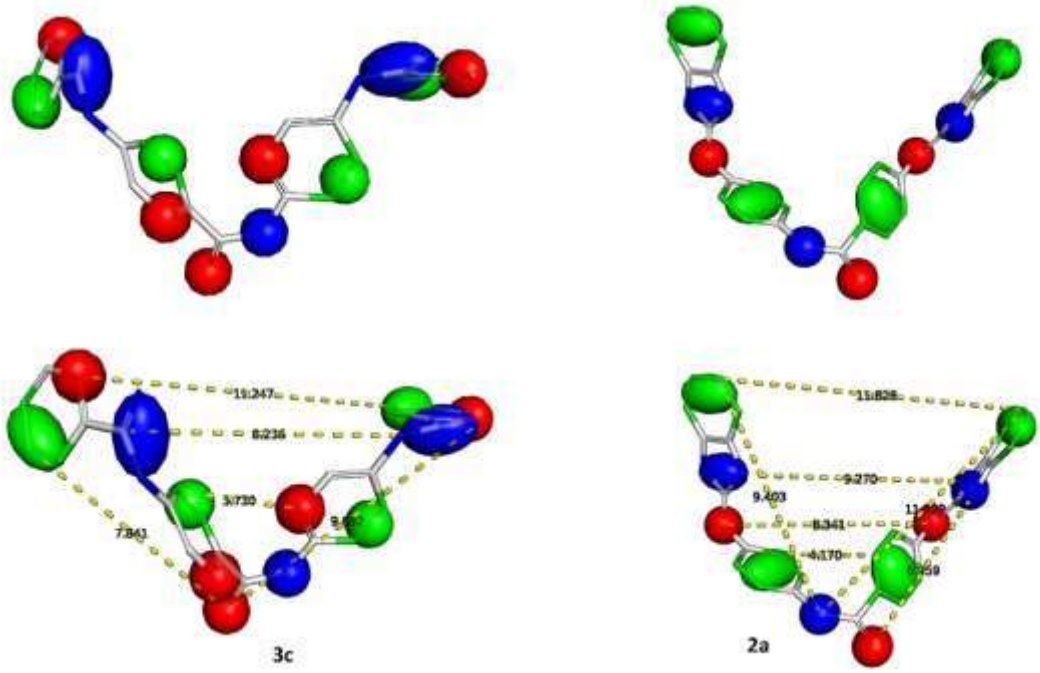


Figure 2: 3D structures featuring the pharmacophore models of the two most and least active molecules, 3c and 2a, respectively.

In the 3c molecule, the greatest distance between the acceptor (Red) and the liphophile (Blue) is 11.247 A0. The maximum distance between the donor and acceptor is 9.832 A0. In the 2a molecule, the greatest distance between the liphophile and the donor is 11.828 A0, while the lowest distance is 4.170 A0.

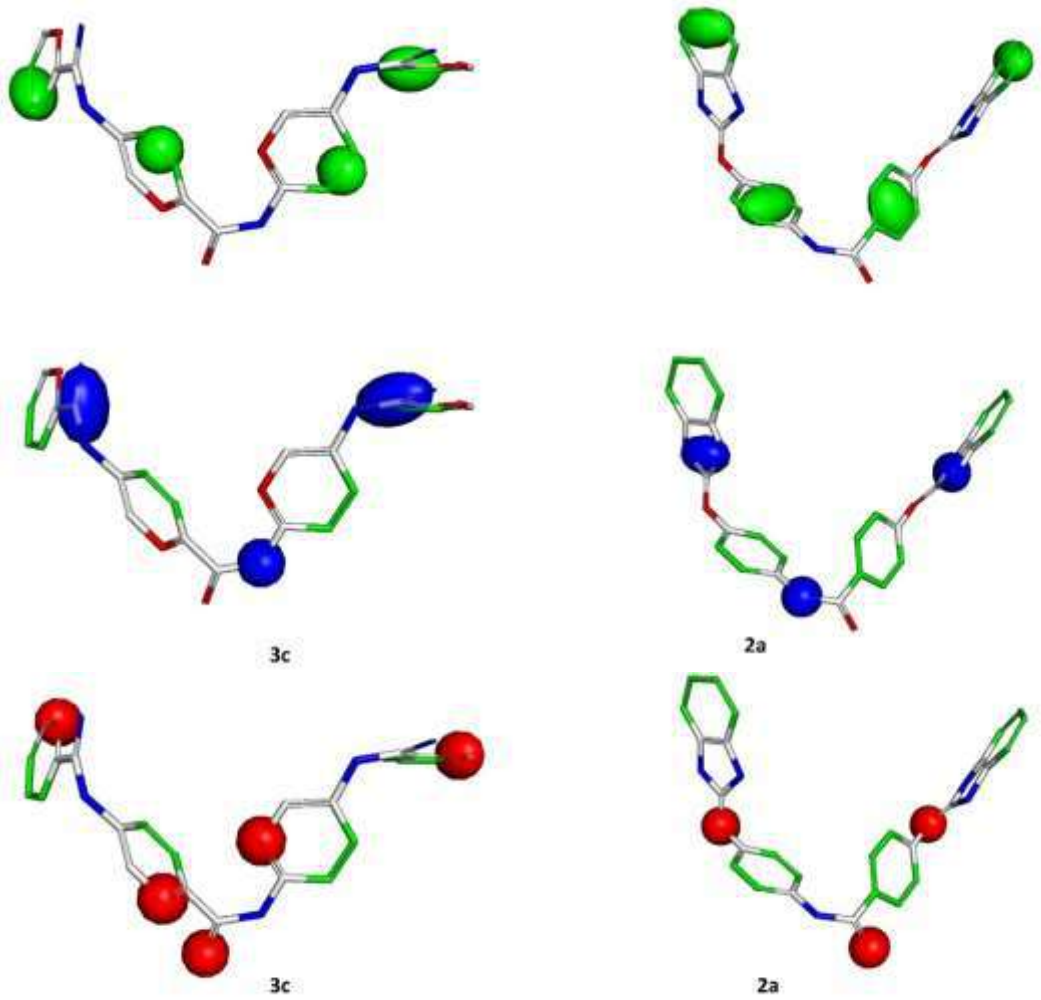


Figure 3: H-bond acceptor (red), lipophilic (green), and H-bond donor (blue) contours for the most active molecule (3c) and the least active molecule (2a).

While 3c and 2a each have five H-bond accepters and three H-bond donors, respectively, in the above figure, both molecules have the same amount of H-bond donors.

Conclusion.

The current investigation shows that H-bond acceptor areas are responsible for the variation in activity. The molecule's different shape could be the second explanation. The pharmacophore portions of most active molecule 3c are closer together than those of least active molecule 2a. Therefore, H-bond acceptors should be prioritized in future optimizations.

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96

Continuous Fixed Bed Adsorption of Heavy Metals Removal Using Granular Activated Carbon

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Abstract:
A comprehensive review is conducted on the effectiveness of several adsorbents in column adsorption for the removal of heavy metals. Included are the fundamental concepts of adsorption, such as chemical and physical adsorption as well as its constituents, adsorbents and adsorbates. The adsorption investigation is examined utilising a range of adsorbates, specifically heavy metals (Cr, Ni, and Cu). For the removal of heavy metals, a number of different design experiments for column adsorption are thoroughly explored. References are given about the column adsorption studies. In-depth explanations of several parameters for column adsorption are provided in this work. All of the relevant parameters are covered, including contact time, pH, temperature, and adsorbent dose for column adsorption and inlet ion concentration, flow rate, and bed height for column adsorption.
Keywords: Adsorption, Column Study, Heavy Metal ions.

Introduction:

Pollutants that alter or interact with groundwater can have an impact on its physical and chemical properties, making it a crucial resource for drinking water, agriculture, and industry worldwide. A study conducted between 2006 and 2009 on 335 productive groundwater wells in the Assuit governorate, Egypt, found that more than 20% of the total wells studied had concentrations of $Ca^{2+,}$ Na^{+}, Mg^{2+}, K^{+}, HCO^{3-}, Fe, and SO_4^{2-}above the permissible legislative limits for drinking water standards set by the World Health Organization (WHO).[1] Several solutions had been introduced to minimize the levels of these pollutants. For examples; using aeration, sedimentation with/without coagulants , ion exchange and biofilteration [2], [3] technology to remove iron and manganese [4]. The process of adsorption involves moving chemicals from the gaseous or liquid phase onto the adsorbent surface.[5] There is common adsorbent have been extensively studied and commercialized such as silica gel, activated alumina and activated carbon. Activated carbon is the main adsorbent that are used for the water treatment [6].The various adsorbent study is sawdust [7], carbon aero gel [8], herbaceous peat [9], fly ash [10], modified clay [11].Also, some adsorbents studied for copper ions removal via fixed-bed adsorbent such as coconut-shell [12], chitosan immobilized bentonite [13], zeolite/cellulose acetate blend fibre [14] and rice husk-based activated carbon [15] were published. Another researcher attempted to eliminate Nickel ions using activated carbon extracted from sugarcane bagasse [16] and tea factory waste [17]. In summary, adsorption is more beneficial compared to other water treatment techniques available as it is easy to operate, lower cost of operation and simplicity of design [18].Column adsorption provide information on adsorption study with different of adsorbent used. The main objective of this study was to remove Heavy Metal ions from aqueous solution through column study.

Result and Discussion:

Column Study Using Granular Activated Carbon.

Column studies were carried out by using a glass column as designed earlier to see the change or any differences compared to batch experiments, because in industry wastewater treatment are carried out through fixed bed activated carbon columns. The adsorption studies

were carried out single solute component system using a glass column. In present work for the column study the raw GAC and the modified carbon was used. The glass column used in the present investigation contained standard amount of RGAC (Raw Granular Activated Carbon) and MGAC (Modified Granular Activated Carbon) modified carbon using Oxidizing agent and then metal ion solutions were passed through it maintaining a constant flow rate. This experiment was carried out to see the saturation level of the raw granular activated carbon for metal ion solution. For Cobalt metal ion it was observed that when the varying (increasing) volume of Cobalt solution was passed through the column then tendency of adsorbing of the carbon increases.

TABLE-1
Column study for adsorption of Cobalt on F-400 GAC

Sr No	Initial amount of Cobalt in solution in mg/ml	Volume of Cobalt Solution In ml	Final amount of Cobalt in solution in mg/ml	Amount of Cobalt adsorbed by GAC in mg/gm
1	3.65	300	0.4519	3.1981
2	3.65	350	1.2000	2.4500
3	3.65	400	2.2000	1.4500
4	3.65	450	2.8400	0.8100

TABLE -2
Column study for adsorption of Cobalt on F-400 Modified GAC

Sr No	Initial amount of Cobalt in solution in mg/ml	Volume of Cobalt solution in ml	Final amount of Cobalt in solution in mg/ml	Amount of Cobalt adsorbed by modified GAC in mg/gm
1	2.11	300	0.61	1.50
2	2.11	400	0.79	1.32
3	2.11	500	0.86	1.25
4	2.11	600	1.11	1.00

Conclusion :

The present work was initiated keeping in view that the presence of toxic metals in the wastewater, which could lead to serious effect on living things. Adsorption by granular activated carbon is a very effective and economical technique for the removal of these toxic metals from wastewater as seen from literature studies in recent years. Technique was found to be useful in the separation of particular metal ion from the mixture of metal ions. The oxidizing agent such as Nitric acid played an important role in the modification of the carbon surface was found to be better using oxidizing agents compared to use of raw carbon.

It can be concluded that there is an improvement in the overall efficiency of the GAC towards Co(II) due to the presence of the new active functional group in addition to enhancing the chemical stability of the GAC.

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97

Sustainable Production and Analysis of Silver Nanoparticles Using Extract from Portulaca oleracea Leaves for Eco-Friendly Applications

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Abstract:
This study focused on the environmentally conscious synthesis of silver nanoparticles through the use of Portulaca oleracea leaf extract. The eco-friendly nature of the synthesis method aligns with the increasing demand for sustainable and green approaches in nanoparticle production. The study investigates into the detailed characterization of the silver nanoparticles, exploring their unique properties and potential applications. It was found from the kinetic study for formation of silver nanoparticles using aqueous exctract of Portulaca oleracea plant the time required for conversion of silver solution to the brownish yellow coloured silver sol is reduced by carrying of the reaction at ambient pH conditions. The alkaline pH was found to be more suitable pH for the biosynthesis of AgNPs by using plant extract. The broad nature of the spectrum suggests the formation of polydispersed nanoparticles, a characteristic further supported by TEM micrograph analysis.
Keywords: Eco-freindly synthesis, Portulaca oleracea, nanoparticles

Introduction:
In recent years, there has been a growing emphasis on environmentally sustainable practices in the field of nanotechnology, particularly in the synthesis of nanoparticles. The synthesis process using plant extract is often straightforward, involving the mixture of plant extracts with metal salts at ambient conditions.
The plant material is immersed in water, followed by boiling to extract bioactive compounds crucial for nanoparticle formation. Plant extracts serve as excellent reductants and stabilizers, contributing to the low-cost, environmentally friendly, and sustainable nature of the synthesis. The ease of extraction and abundance of plant materials make this method accessible and scalable. The 'green' synthesis approach extends to various metals, including silver, gold, and their oxides, offering versatility in nanomaterial production Each plant species contributes unique phytochemicals, influencing the characteristics of the synthesized nanomaterials.
Studies have reported the successful synthesis of silver nanoparticles using aqueous leaf extracts of Cucumis, showcasing a reliable and cost-effective approach. We reported in our previous work the synthesis of silver nanoparticles (Ag NPs) using an aqueous extract of *Acacia auriculiformis* that acts as reducing agent as well as capping agent.
This research endeavors to contribute to the ongoing quest for eco-friendly approaches by exploring the utilization of Portulaca oleracea leaf extract for the synthesis and characterization of silver nanoparticles. Portulaca oleracea, commonly known as purslane, is recognized for its rich bioactive compounds that may play a crucial role in the reduction and stabilization of silver nanoparticles. Leveraging its inherent properties, this study aims to develop a green and sustainable method for the production of silver nanoparticles, ensuring minimal environmental impact. The subsequent characterization of these nanoparticles will shed light on their physicochemical properties, paving the way for potential applications in various environmentally conscious sectors. Through this research, we aspire to bridge the gap between nanotechnology and ecological responsibility, offering a promising avenue for the development of sustainable materials with diverse practical

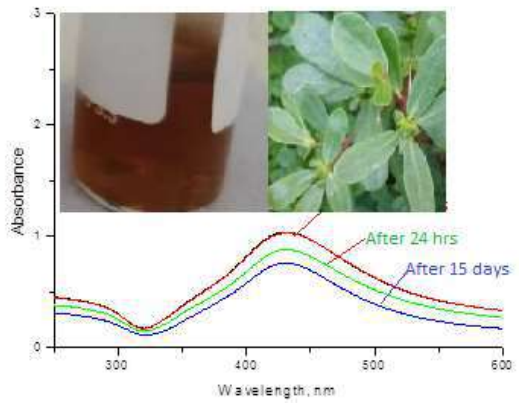
Methodology:
Portulaca oleracea leaves that were dry were procured from local market in Amravati, Maharashtra, India, as needed. To get rid of the dust particles, Distilled water was used to wash the leaves multiple times. Sodium hydroxide (Sigma) and silver nitrate (s.d. fine chem.) were employed as received without further purification. Distilled water was used for the studies. Chromic acid and aqua regia were used to clean the glassware.

a. Preparation of Plant Extract:
In a 250 ml beaker, 5g of cleaned and washed Portulaca oleracea leaves were boiled with 100 ml of distilled water until the volume was reduced to nearly half. The mixture was then cooled and filtered into a 50 ml volumetric flask, with the volume being made up to 50 ml with distilled water. The final extract is refrigerated until needed.

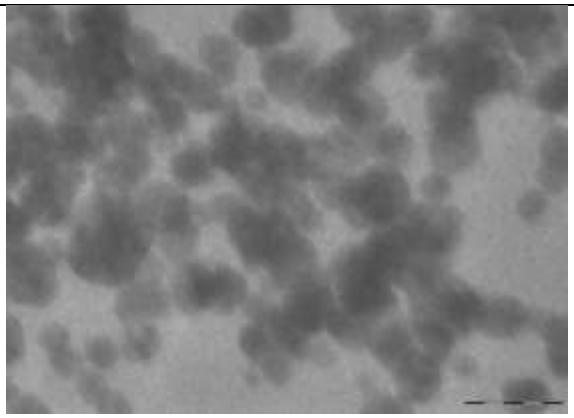
b. Synthesis of Ag Nanoparticles:
In a typical synthesis, 0.5 mM aqueous solution of $AgNO_3$ was mixed with 1 ml plant extract in the absence of stabilizing agent at room temperature. The reaction was carried out at different pH of the solution by adding NaOH solution to study the influence of pH. Changes in the color of solutions indicate the formation of Ag nanoparticles. Formation of stable yellow dispersion was obtained with time.

c. Characterisation:
Measurements of UV-Vis absorption was carried out using a JASCO V-650 spectrophotometer. A JEOL 2000 FX machine running at 200 keV is used to capture transmission electron micrographs. To prepare samples for transmission electron microscopy (TEM), a drop of the colloidal solution was applied to a copper grid that was covered in a thin layer of amorphous carbon and set on filter paper.

Result and Discussions:
As the aqueous leaves extract of Portulaca oleracea leaves were added to silver nitrate solution at the pH ranges from 6-11. The color of the solution changed from pale yellow to yellowish-brown which indicated the formation of AgNPs. The kinetic for the formation of AgNPs was studied at different pH of the solution. It was found that the kinetic parameters for biosynthesis of AgNPs varied with the pH of the solution. The optimum pH for the formation of AgNPs was found to be pH 10 Which indicates alkaline nature of the solutions speed up the nucleation process attributed to activation of polyphols present in the Portulaca oleracea leaves extract as evident in the leterature. UV–Vis spectra of the AgNPs with the aqueous leaf extract give a sharp peak at 430 nm after 20 min incubation (Figure 1a) at pH 10.5. One of the most used methods for characterizing a nanoparticle's structure is UV–visible spectroscopy. The development of AgNPs in the solution as a result of surface plasmon resonance (SPR) electrons on the nanoparticle surface is amply demonstrated by the existence of an absorbance peak at roughly 420 nm. The size, shape, and dielectric properties of the synthesis medium, as well as the interactions between the individual metal particles and their inter-nanoparticle coupling, all influence the SPR pattern. The broad nature of spectrum indicates the formation of polydispersed nanoparticles which is further evident by TEM micrograph as shown in Figure 1b. The average size of the silver nanoparticles was found to be 27nm. Further study is going on to see their applications in control of bacterial growth.



(a)



(b)

Figure 1: a)UV–Vis spectra of Ag nanoparticles prepared with aqueous extract of Portulaca oleracea plant leaves using 0.5 mM $AgNO_3$ and 1 ml of plant extract at pH 10.5 without using any stabilizing agent. Inset: Photograph of AgNPs and Leaves of Portulaca oleracea. Path length of cell 1 cm. b) TEM image of Ag nanoparticles.

Conclusions:

The aqueous leaf extract of Portulaca oleracea leaves successfully mediated the biosynthesis of silver nanoparticles. The reaction parameters such as pH of the solution play important role in reduction process silver ions by the polyphenols of the plant extract. These findings underscore the potential use of Portulaca oleracea leaves extract for the synthesis of silver nanoparticles. The Portulaca oleracea, known for its medicinal and nutritional attributes, contributes to the synthesis process, adding a biocompatible aspect to the nanoparticles. The research provides insights into the green synthesis technique and the promising characteristics of the resulting silver nanoparticles, paving the way for sustainable nanomaterial applications.

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98

Studies in the Synthesis of 5-(3-Substitutedthiocarbamido) Aminoindole by Microwave Technique

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Abstract:
We reported synthesis of 5-(3-thiocarbamido)aminoindol, 5-(3-allylthiocarbamido) aminoindole, 5-(3-*o*-nitrophenylthio- carbamido) aminoindol, 5-(3-*p*-nitrophenylthiocarbamido) aminoindol, 5-(3-*m*-chloro- phenylthiocarbamido)aminoindole by interacting 5-chloroindol with thiourea, allyl thiourea, *o*-nitrophenylthiourea, *m*-chlorophenylthiourea respectively. Ethanol was taken and kept in microwave oven and irradiation was carried out for 2 minutes at 50 °C. The justification and determination of structures of synthesized molecules were done on the basis of elemental analysis, chemical characterizations, IR, H^1-NMR, C^{13}NMR studies.This green synthetic method increases yield of products by maintaining the purity of the products this is the novelty of the research work.
Key words: 5-chloroindole, substituted thiourea, green synthesis, microwave technique.

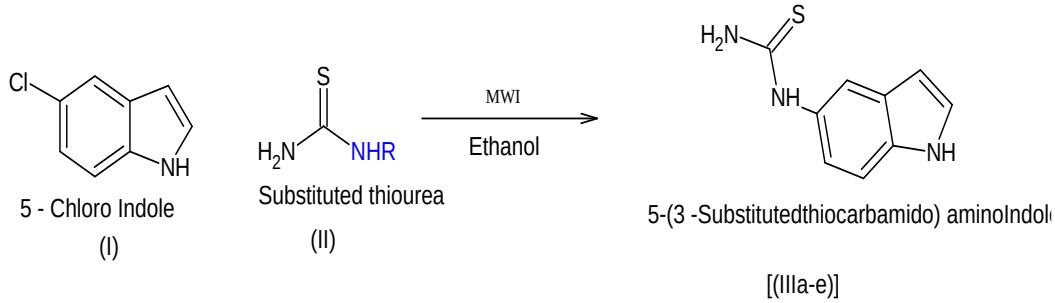
INTRODUCTION

Indole nucleus containing heterocycles created their own identity due to these applications in life, pharmaceutical, medical, and agricultural sciences. Indoles showed anticancer, anti-inflammatory, antioxidant activities[1-3].

Indole based heterocycles are well known recognised for their antimicrobial, anti-micotic and inhibition of chemical mediator's release[4], anti-inflammatory[5-7], anti-asthama[8], anti-vascular[9], antifungal[10], activities.At the same time thiocarbamido nucleus showed antioxidant, anticancer, anti-inflammatory antitubercular activities. Majority of alkaloids contain indole nucleus which exhibits excellent biological activities i.e.antiviral, antitumor, antiplasmodial, antibacterial and neurochemicals melatonin and serotonin are more complex bisindole natural products vincristine and vinblastine these are the key structural component of many effective synthetic pharmaceuticals[4-5].Amino acid tryptophans, the biogenic amines serotonin, tryptamine and the mammalian hormone melatonin are broadly known indole derivatives play an significant role in lively activity of humans and animals[11].

Synthetic applications of cynoguanidine and 1, 3- diformamido-thiocarbamide had been briefly explored[12]. Synthesis of nitrogen, sulphur and nitrogen and sulphur containing heteroacycles and heterocycles the interactions of cynoguanidine with various thiourea and isothiocynates have been investigated in sufficient details [13-18]. Some of these compounds showed remarkable pharmaceutical and biological activities[19-20]. As a wider programme of this research laboratory we have decided to synthesize a novel series of 5-(3-substituted thiocarbamido) aminoindole by interacting 5-chloroindole (I) with thiourea (IIa), allyl thiourea (IIb), *o*-nitro-phenyl thiourea (IIc), *p*-nitro-phenyl thiourea (IId), *m*-chloro-phenyl thiourea(IIe) in presence of ethanol by using microwave technique. Structure determination and identification of the synthesized product is done on the basis of chemical characteristics, elemental analysis and spectral data.

GENERAL REACTION:-



Where R= -H, -allyl, -*o*-nitrophenyl, -*p*-nitrophenyl, *m*-chlorophenyl

2. EXPERIMENTAL

The melting point of the allsynthesized compounds was recorded using hot paraffin bath. The carbon and hydrogen analysis were carried out on Carlo-Ebra 1106 analyzer. Nitrogen estimation was carried out on Colman-N-analizer-29. IR spectra were recorded on Perkin Elmer Spectrometer in range 4000-400cm^{-1} in KBr pellets. The purity of compound was checked by TLC plate. All chemicals used were of AR-grade.

2.1 5-(3-Thiocarbamido) Amino Indole (IIIa)

A mixture of 5-chloroindole (I) (0.1M, 0.392 gms) and thiourea (0.1M, 0.152 gms) in ethanol was kept in microwave used to synthesis 5-(3-thiocarbamido) amino indole (IIIa) (1 gm, 97.35%), melting point 160^{0}C.(D)

RESULTS AND DISCUSSION

Properties of (IIIa): It is pale yellow colour crystalline solid having melting point 160^{0}c (D). It gave positive test for nitrogen and sulphur. Desulphurised with alkaline plumbite solution. It forms picrate, melting point 120^{0}c. Elemental analysis C {(found 67.58%) calculated 68.30%}, H {(found 5.17%) calculated 5.33%}, N {(found 14.86%) calculated 14.94 %}, S {(found 11.24%) calculated 11.38%}.

IR Spectra

FTIR Spectrum was recorded using KBr-pellets and is reproduced. Important absorption can be correlated as (cm^{-1}): N-H stretching at 3387.00cm^{-1} (3500-3000 cm^{-1}), Ar-H stretching at 2690.70cm^{-1} (3000-2500cm-^{1}), Ar-c=c stretching at 1612.49cm^{-1} (1600-1500cm^{-1}), C-N stretching at 1085.92cm^{-1} (1200-1000cm)$^{-1}$, N-C=S stretching at 1462.04cm^{-1} (1550-1250cm^{-1}), NN>C=S stretching at 1400.89cm^{-1} (1400-1200cm-1).

NMR

This spectrum distinctly displayed signals at (δ ppm): signal at 7.2646-7.1726 ppm is due to Ar-H, signal at 4.2911-4.4564 ppm is due to N-H in aromatic ring, signal at 3.1402-2.2160 ppm is due to NH_2 and -NH protons. ^{13}C Spectrum: This spectrum distinctly displayed signals due to C=S carbon at δ 181.76 ppm, Ar-C carbon at δ 155.58-112.58 ppm, -CH_2 carbons at δ 79.04-78.38 ppm, -CH_3 carbons at δ 4012-38.87 ppm.

2.2 5-(3-Allylthiocarbamido) Amino Indole (IIIb)

A mixture of 5-chloroindole (I) (0.1 M, 1.56 gm) and allyl thiourea (IIb) (0.1 M, 0.68 gm), in ethanolwas kept in microwave used to synthesis 5-(3-allylthiocarbamido) amino indole (IIIb) (2 gm, 90%), melting point 186^{0}C.(D)

RESULTS AND DISCUSSION

Properties of (IIIb): It is lemon yellow colour crystalline solid having melting point 186^{0}c (D). It gave positive test for nitrogen and sulfur. Desulphurized with alkaline plumbite solution. It forms picrate, melting point 110^{0}c. Elemental analysis C {(found 68.58%) calculated 69.27%}, H {(found 5.11%) calculated 5.35%}, N {(found 15.86%) calculated 16.64 %}, S {(found 11.34%) calculated 11.48%}.

IR Spectra

The IR spectra was carried out in KBr pellets and the important absorptions can be correlated as, (cm^{-1}) 3312 (N-H stretching), 1197 (C-N stretching), 3012 (Ar-H stretching), 1736 (N=C-N stretching), 1512 (Ar-C=C), 1487 (N-C=S) Bending.

NMR

Ar-H protons (6.8720-6.8991 ppm), N-H protons (5.0417-5.0471 ppm), N-H of five membered ring (4.2921-4.5564 ppm), -CH3 protons (3.4386-3.8638 ppm).

2.3 5-(3-*o*-nitro-phenyl thiocarbamido) Amino Indole (IIIc)

A mixture of 5-chloroindole (I) (0.1 M, 1.17 gm) and *o*-nitro-phenyl thiourea (IIc) (0.1 M, 1.212 gm), in ethanol was used to synthesis 5-(3-*o*-nitro-phenylthiocarbamido) amino indole (IIIc) (3 gm, 94%), melting point 192^0C.(D)

RESULTS AND DISCUSSION

Properties of (IIIc)-It is orange colour crystalline solid having melting point 192^0c (D). It gave positive test for nitrogen and sulphur. Desulphurisd with alkaline plumbite solution. It forms picrate, melting point 120^0c. Elemental analysis C {(found 63.58%) calculated 64.27%}, H {(found 5.91%) calculated 6.35%}, N {(found 15.06%) calculated 16.64 %}, S {(found 11.34%) calculated 11.48%}.

IR Spectra

The IR spectra was carried out in KBr pellets and the important absorptions can be correlated as, (cm^{-1}) 3312 (N-H stretching), 1197 (C-N stretching), 3012 (Ar-H stretching), 1736 (N=C-N stretching), 1512 (Ar-C=C), 1487 (N-C=S) Bending.

NMR

Ar-H protons (6.8720-6.8291 ppm), N-H protons (5.0417-5.0471 ppm), N-H of five membered ring (4.2920-4.5565 ppm).

2.4 5-(3-*p*-nitro-phenyl thiocarbamido) Amino Indole (IIId)

A mixture of 5-chloroindole (I) (0.1 M, 1.16 gm) and *o*-nitro-phenyl thiourea (IId) (0.1 M, 1.26 gm), in ethanol was used to synthesis 5-(3-*p*-nitro-phenylthiocarbamido) amino indole (IIId) (2.9 gm, 94%), melting point 194^0C.(D)

RESULTS AND DISCUSSION

Properties of (IIId)-It is pale orange colour crystalline solid having melting point 194^0c (D). It gave positive test for nitrogen and sulphur. Desulphurisd with alkaline plumbite solution. It forms picrate, melting point 130^0c. Elemental analysis C {(found 63.98%) calculated 64.57%}, H {(found 4.91%) calculated 5.59%}, N {(found 15.26%) calculated 16.97 %}, S {(found 11.34%) calculated 11.78%}.

IR Spectra

The IR spectra was carried out in KBr pellets and the important absorptions can be correlated as, (cm^{-1}) 3612 (N-H stretching), 1097 (C-N stretching), 3092 (Ar-H stretching), 1796 (N=C-N stretching), 1572 (Ar-C=C), 1447 (N-C=S) Bending.

NMR

Ar-H protons (6.8420-6.8491 ppm), N-H protons (5.0417-5.0471 ppm), N-H of five membered ring (4.2960-4.5566 ppm).

2.5 5-(3-*m*-chloro-phenyl thiocarbamido) Amino Indole (IIIe)

A mixture of 5-chloroindole (I) (0.1 M, 1.36 gm) and *m*-chloro-phenyl thiourea (IIe) (0.1 M, 1.09 gm) in ethanol was used to synthesis 5-(3-*m*-chloro-phenylthiocarbamido) amino indole (IIIe) (2.4 gm, 95%), melting point 193^0C.(D)

RESULTS AND DISCUSSION

Properties of (IIIe)-It is ivory colour crystalline solid having melting point 193^0c (D). It gave positive test for nitrogen and sulphur. Desulphurisd with alkaline plumbite solution. It forms picrate, melting point 180^0c. Elemental analysis C {(found 62.98%) calculated 63.57%}, H

{(found 4.31%) calculated 5.89%}, N {(found 14.26%) calculated 15.97 %}, S {(found 11.24%) calculated 11.94%}.

IR Spectra

The IR spectra was carried out in KBr pellets and the important absorptions can be correlated as, (cm^{-1}) 3412 (N-H stretching), 1037 (C-N stretching), 3192 (Ar-H stretching), 1996 (N=C-N stretching), 1672 (Ar-C=C), 1457 (N-C=S) Bending.

NMR

Ar-H protons (6.9420-6.8491 ppm), N-H protons (5.0417-5.0461 ppm), N-H of five membered ring (4.2760-4.5596 ppm).

ACKNOWLEDGMENTS

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99

Study of Physico-chemical Parameter of Soil Analysis in Buldhana district

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Abstract:
The soil is a mixture of solid, water and gases and also a mixture of minerals, organic matter, gases, liquid and other macro or microorganisms and it performs four important functions. The basic of the status of soil we decide requirement of fertilizer to increase the fertility of the soil. This work examines the principal physical and chemical attributes that can serve as indicators of a change in soil quality under particular agro-climatic condition. You will find that different soil can vary greatly in their composition. Proposed indicator including soil depth to a root restricting layer, water holding capacity, organic matter, N, P, K, Cl, electrical conductivity, moisture content. We also confirmed the justification for selecting these key attributes, their measurement, critical limit for monitoring change in solid productivity and soil quality and crop growth in that soil.

Keywords: Physico chemical Parameter pH.

INTRODUCTION

Soil is a complex collection of Organic and Inorganic matter. Soil is called the layer of the Earth and involve lithosphere, hydrosphere, atmosphere & biosphere. pedolith, used to prefer to the soil, content translates ground stone. it consists of a solid phase of minerals, organic matter, and porous phase that holds the soil moisture with water. respectively, soils are often treated as system of solids, liquids, and gases. Soils are Consist of mineral and organic particles of various sizes. The particles are associated in a matrix with results in about 50% porous; it is filling up with water and air. This will prepare a three-phase system of solids, liquids, and gases, all uses of soils are greatly affected by physical properties. Plants need certain nutrient elements to complete their life cycle. No element can substitute for the same.16 elements are essential for the growth of most vascular plants. Carbon, hydrogen, and oxygen are combined in photosynthesis reactions and are obtained from air and water. These three elements compose 90 % of the dry matter of plants. The remaining is obtained largely from the soil and is referred to as the macronutrients.[1-3]

FACTORS AND PROCESSES

This is accomplished by disintegration &decomposition It is related with the action of Soil Factors 2.1 Factors The soils develop as a result of the action of soil forming factors S = f (P, Cl, O R, P, T) Further, Jenny (1941) formulated the following equation Where, Cl – environmental climate O – Organisms and vegetation (biosphere) R – Relief or topography P – Parent material T- Tim

METHODOLOGY

Area of Study Keshav Shivani village is situated on the nearby Samrudhi mahamarg Dusarbid. There is more forestry area around the village. It is about 80k.m. away from Buldana inSindhkhedraja Tehsil dist. Buldana. Buldana is one of the five Districts of Amravati division of Vidhrabh region of Maharashtra near satpuda mount. Mostly Agriculture crop is found in Keshav Shivani village is as follows Jawar, chili, wheat, soybean but now a day's mostly soyabin crops , out of these cotton is one of the most important crop in Keshavshivani village Various type of soil is present in Dasala 1. Lime soil 2. Black cotton soil 3. Red soiletc. The collected soil samples analysis kit platform available in Laboratory department of Chemistry,

soil samples are proposed to collect from the farms of following farmers at Keshavshivani village.

Sr.No	Name of Farmer	Sample Collected
1	Bandu Shivaji Ghuge	Farm
2	Swapnil Raju Gutthe	Farm
3	Raju Martand Gutthe	Farm
4	Dilip M. Mahadik	Farm
5	BajiroU.Wagh	Farm

EXPERIMENTAL PROCEDURE

Procedure: Add 25 ml distilled water to 10 g air-dried sample in a beaker 50 ml. Read the suspension temperature by thermometer. Stir at regular intervals for 20-30 minutes. Wash the pH meter electrode with distilled water. Open the contact switch, wait 5 minutes, adjust temperature knob to room temperature. Rinse the electrode with distilled water, then with the soil suspension after stirring. Read the pH value of the soil suspension. 3.2 Electrical Conductivity (EC) Electrical conductivity is commonly used for measuring the electrical resistance in the solution which indicates the total concentration of ionized constituents in solutions. It is closely related to the sum of the cations and anions in the suspension. Accordingly, it can be used for indicating the salinity in soil extracts. Electric conductivity can be expressed as milliohms/cm in 11:215 soil/water extract. Reagents: 1- Potassium chloride solution 0.01N: 2- Calcium sulphate dehydrates saturated solution. Procedures: Extraction: Take 10 g air-dry soil in 100 ml beaker, add 25 ml distilled water Stir for 10 minutes, and repeat stirring 4 times on 30 minutes intervals Measure the suspension temperature by thermometer read out the electrical conductivity of soil solution

Total Nitrogen Reagents: 1. Digestion mixture: Mixture of Potassium sulphate K2SO4 and Copper sulphate CuSO4. 5H2O. with Selenium. Mixed with proportion of 10: 1: 0.5 respectively. 2. H2SO4 conc. 3. NaOH solution (40%). 4. H_3BO_3 solution (4%). 5. 0.01 N HCl 6. Indicator Procedure: Weigh 5 g soil into digestion flask add 5 g digestion mixture and 20 ml Conc. H2SO4 put the flask on digestion board with electric heaters. Heat gradually; low at 10-30 minutes, then raise heating degree. After the end of fuming, the digestion is continued for 1 hour after the solution had cleared with white colour of digestion mixture. Transfer the sample to 250 ml volumetric flask; complete the volume with dist. Water. Distillation: Put 20 ml H_3BO_3 in Erlenmeyer flask and 4 drops of the indicator. Put the flask so that the lower tip of the glass receiver tube is below the boric acid surface. Start running the cooling water in condenser boils the water in the boilers. Put 25 ml of the sample in the funnel with dist. Water. Released ammonia is trapped in boric acid. Titration: Ammonia is titrated with HCl or H_2SO_4. at end point the green colour just disappears. Calculation N % in soil = ( )× ×× 3.4 Soil Organic Matter

2- Add 10 ml of 1 N K2Cr2O7 by means of a pipette. Add 200 ml of concentrated H2SO4 by means of dispenser and swirl gently to mix. Allow to stand 30 minutes. The flasks should be placed on an asbestos sheet during this time to avoid rapid loss of heat. Dilute the suspension with about 200 ml of water to provide a clearer suspension for viewing the endpoint. 3- Add 10 ml of 85% H3PO4, using a suitable dispenser, and 0.2 g of NaF, using the spatula The H3PO4 and NaF are added to complex Fe3+, which would interfere with the titration endpoint. Add 10 drops of ferroin indicator. 4- Titrate with 0.5 N Fe++ to a burgundy endpoint. The colour of the solution at the beginning is yellow-orange to dark green, The reagent blank is used to standardize the Fe++ solution daily. Calculate % C and % organic matter % easily oxidizable organic C C =()×× × × 100 Where: B = ml of Fe++ solution used to titrate blank, S = ml of Fe++ solution used to titrate sample, and 12/ 4000 = mill equivalent 3.5 Moisture Content Procedure: Weigh 5.00 g of air-dry soil < 2 mm into a previously dried (at 105o C)

and weighed weighing dish with lid (a labelled aluminium dish) fit lid, cool in a desiccators for at least 30 minutes and reweigh. All Weighing should be recorded to 3 decimal places. Calculation: % moisture = () \ () ×100 Chloride: - Reagents A. Potassium Chromate, Silver Nitrate Solution (AgNO3) 0.01N NaCl, 0.01 N Procedure: Pipette 5-10 ml soil saturation extract into a wide-mouth porcelain Crucible or a 150-ml Erlenmeyer flask. Add 4 drops potassium chromate solution. Titrate against silver nitrate solution until a permanent reddish-brown color appears. Always run two blanks containing all reagents but no soil, and treat them in exactly the same way as for the samples. Subtract the blank titration reading from the readings for all samples. Calculation (V - B) × N × R × 1000 Cl (meq/L) = Wt 3.7 Water Holding Capacity Procedure: Weight accurately 20 gm of soil sample on the balance transfer this soil on the Whitman's filter paper and kept this soil in funnel then on the measuring cylinder pour 40 ml of water into the soil sample Keep this experiment stay for one night Then observe how much of water is come down from soil sample in measuring cylinder accurately weight the wet soil with filter paper and subtract weight of filter paper from wet soil Then calculate the water holding capacity by the using below formula WHC = weight of wet soil – weight of taken soil[4]

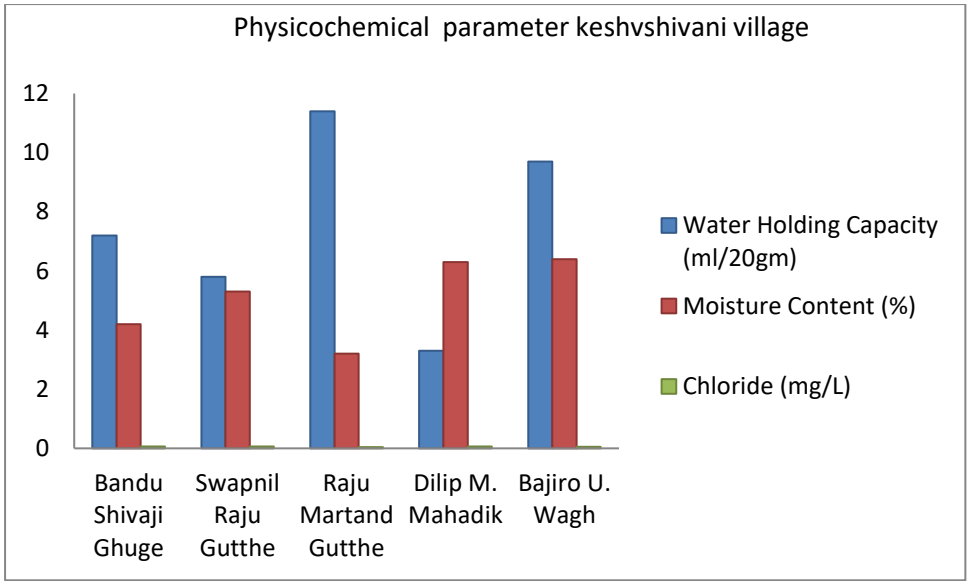
RESULT AND DISCUSSION

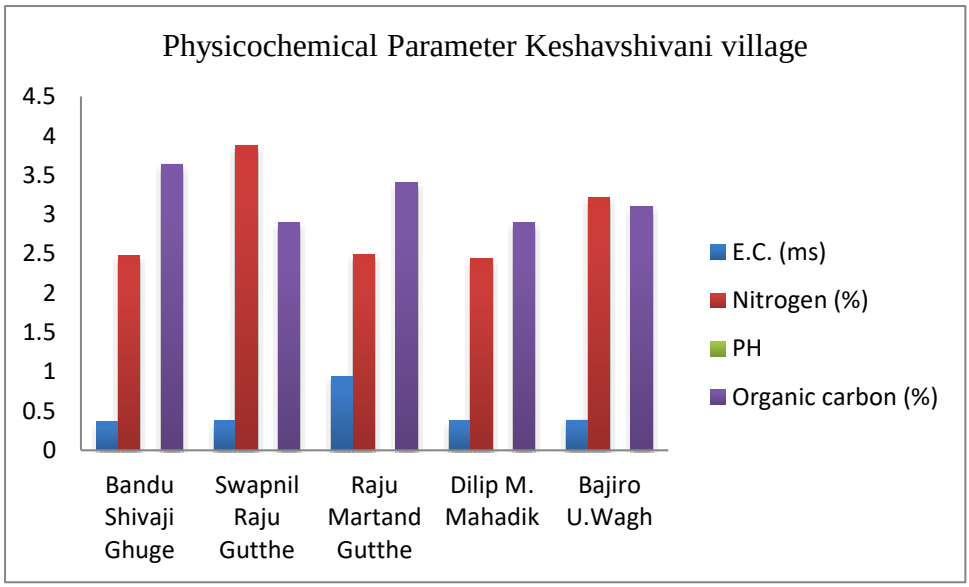
Temperature of Soil sample was found to be 28.9 to 34.7 2. Colour of Soil sample found to be Black, Lime and red and amount of pH present in the Soil sample was found to be in between range of 6.2 to 8.32 4. The amount of chloride ion present in the Soil sample was found to be in between 0.047 to 0.093 mg/L

Fig-1.1 Physicochemical Parameter of five different location of keshashivani Village.

Sr. No.	Name of Parameter			
	Name of Farmer	Water Holding Capacity (ml/20gm)	Moisture Content (%)	Chloride (mg/L)
1	Bandu Shivaji Ghuge	7.2	4.2	0.064
2	Swapnil Raju Gutthe	5.8	5.3	0.068
3	Raju Martand Gutthe	11.4	3.2	0.042
4	Dilip M. Mahadik	3.3	6.3	0.058
5	Bajiro U. Wagh	9.7	6.4	0.057

Sr. No.	Name of Parameter				
	Name of Farmer	E.C. (ms)	Nitrogen (%)	PH	Organic carbon (%)
1	Bandu Shivaji Ghuge	0.361	2.48	7.30 at 24^0 C	3.64
2	Swapnil Raju Gutthe	0.374	3.88	7.43 at 24^0 C	2.9
3	Raju Martand Gutthe	0.938	2.49	8.20 at 24^0 C	3.40
4	Dilip M. Mahadik	0.376	2.44	7.50 at 24^0 C	2.90
5	Bajiro U.Wagh	0.384	3.22	8.10 at 24^0 C	3.1





CONCLUSION- The study of soil is mostly based on the following parameter of soil which is as follows A) Texture B) Fertility C) Colour D) Moisture E) Water holding capacity Soil analysis of Keshavshivani village found that soil of Keshavshivani village is blackish in nature which posses good water holding property & moisture as well as organic carbon beyond that found soil of Keshavshivani village has necessary nitrogen on the basis of above data we can assume that the soil of Keshavshivani village has good fertility for the following crops Soyabean, Wheat, Blackgram, Greengram, Cotton.

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100

Formulation and Evaluation of Chitosan Nanoparticle Based *In-Situ* Nasal Gel For Parkinson's Disease

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Abstract:
Parkinson's disease is a chronic progressive neurodegenerative disease. As the disease affects the central nervous system drug delivery has to cross BBB. Intranasal delivery to brain via olfactory region is best way to treat CNS diseases. Here we formulated chitosan nanoparticles by ionic gelation technique which then incorporated into the *in-situ* nasal gel. Poloxamer 407 at the 20% conc.is best for thermosensitive gelling mechanism. Batch F8 of nanoparticles were optimized by considering the Particle size (**112.9±1.30**), PDI (**0.353±0.013**), Zeta potential (**28.36±2.58**),%Entrapment efficiency of Levodopa (**94.03±3.02**) and % Entrapment efficiency of Selegiline HCL(**58.01±1.97**).Levodopa-selegiline HCL chitosan (LD-SLG-CS) nanoparticle based *in-situ* nasal gel was formulated by taking the batch F8 and it was found to be clear and had pH of **6.3**, gelling temp. of **30 ± 0.6 ^{0}C**, drug content of Levodopa in formulation was **92 ± 0.84 %** while of selegiline HCL was found **88 ± 0.45 %.** *In-vitro* release of LD-SLG-CS nanoparticle based in-situ nasal gel for drug Levodopa followed Higuchi kinetics and selegiline HCl followed zero order kinetics. Ex-*vivo* permeation study for 7 hours showed that Levodopa and selegiline HCl had 28.229 and 65.055 % cumulative release respectively. *In-vivo* pharmacodynamic study on female wistar rats were performed; in that locomotion activity by open field test, grip strength and akinesia test had significant results which indicates that formulation had dynamic effect on the Parkinsons disease.

Keywords: Parkinson's disease, Chitosan nanoparticles, *in-situ* nasal gel, Levodopa, Selegiline HCl**.**

Introduction

Parkinsons disease as a "shaking palsy",it is a chronic, progressive neurodegenerative disease characterized by both motor and nonmotor features. This disease significantly through the degenerating effects of disease on patients movement daily activity and normal routine behavior. Parkinsonism is not related to single characteristic of disease; it is the set of some complex symptoms which include the muscle rigidity,bradykinesia and resting tremors.It is believed that caffeine, ciggarate smoking and statins mitigate the risk of Parkinson's disease.

Other Conventional preparations have various limitations like high dose low bioavailability, first pass metabolism, instability etc. to overcome these limitations its need to use novel drug delivery systems like nanoparticles. Parkinson's disease requires the direct delivery of drug to brain hence intranasal route is preferred as the olfactory region of the nasal epithelium and the trigeminal neural region are two direct nose to brain pathways. *In-situ* nasal gel is best approach for effective delivery of drug to brain.

Material and Methods

API: Levodopa received as a gift sample,Selegiline Hydrochloride purchased from Himedia. Polymer : Chitosan (LMW); Cross Linking Agent: Sodium Tripolyphosphate purchased from the Sigma Aldrich, Gelling agent: Poloxamer 407 also purchased from Sigma

Aldrich ; Other Agents: Acetic Acid , Potassium Dihydrogen Phosphate , NaOH, etc. received from department store, dialysis membrane purchased from Himedia laboratory.

Preparation of Levodopa Selegiline loaded Chitosan nanoparticles (LD-SLG-CS-NP) Ionotropic gelation Technique

Here firstly Chitosan dissolved in 1% acetic acid. To the chitosan solution 0.5% Tween 80 was added.The pH was adjusted to 5.5 by using 5N NaOH. Solution of Sodium tripolyphosphate (STPP) 0.1% also prepared simultaneously. Levodopa 42 mg and Selegeline HCL 8 mg were added to chitosan solution. Both the drugs were allowed to dissolve completely in this solution. Chitosan-Levodopa-Selegiline (CS-LD-SLG) solution kept for stirring on magnetic stirrer.The solution of STPP was added to the Chitosan solution dropwise at a speed of 2 ml/min by needle. The stirring was allowed for 30 minutes, then homogenization by High Shear Homogenizer.The nanoparticles so formed centrifuged at 4^0 C at 12000 rpm for 30 min in REMI CENTRIFUGE. Pellets formed at bottom were removed and washed with mannitol 2% solution and kept for lyophilization in Freeze dryer. Finally free flowing lyophilized powder obtained.

Preparation of Thermosensitive in-*situ* nasal gel: Nasal *in-situ* gel was prepared by Cold method. Initially in a very small quantity of water, poloxamer dissolved separately in a conc.of 20% w/v at cold condition. Then HPMC dissolved in the quantity as specified in the composition table. Later APIs, PEG 400 and methyl paraben were added and stirred until clear solution was obtained. Finally made volume up to 100 ml with dist.water and kept it overnight at freezing conditions (4 - 10 °C).

Characterization of nanoparticles:

1. **FT-IR studies**
2. **DSC studies**
3. **Average Particle Size and Polydispersity index**
4. **Zeta potential**
5. **Drug% EE**
6. **Surface Morphology**

Evaluation of *in-situ* nasal gel:

1.Clarity:
2.pH of gel:
3.Measurement of Gelation Temperature:
4.Drug Content Estimation:
5..Gel Strength:
6.Viscosity:
***7.In-Vitro* diffusion study:**
***8.Ex-vivo* permeation study:**
***9.In*-vivo study:**

Experimental Design

Animals were randomly assigned into 3 groups. Each group contained 3 animals.
Group 1: Vehicle group (Naive Group) labeled as N1, N2 and N3
Group 2: Disease control group to which Reserpine 1 mg/ kg was given and labeled as H, B and T.
Group 3: Test group to which nanoparticle loaded *in-situ* nasal gel 50 micro-liters + Reserpine 1 mg/kg was given labeled as U1, U2 and U3.

Induction of Parkinson's disease in rat: Reserpine was dissolved in glacial acetic acid (GAA) and then volume adjusted by using dist.water. Reserpine was administered to rats (1 mg/kg,

s.c.) by each alternate day for 3 days i.e. on 1st, 3rd and 5th day and formulation was administered daily for 5 days.The induction of PD was observed by performing various behavioral tests.

Behavioral studies :All behavioral tests were performed on day 1st before the administration of drug and induction of Parkinson's disease. The studies were carried out in a silent and dimly lit room.

10. Stability Study: Stability studies were conducted to test the physical and chemical stability of the developed in situ nasal gel. A sufficient quantity of in situ gel, in screw capped vials was stored at different temp condition as 5 ± 3 °C for 3 month. The physical stability, including appearance, color, pH, sol-gel temp, viscosity, and drug content was studied.

Result and Discussion

Characterization of Nanoparticles

1. **FTIR study:** FT-IR spectrum of Levodopa and Selegiline HCl were taken and it was observed that both drugs having similar spectrum as that of their standard spectrum so it conclude that both drugs were pure. FT-IR spectrum of lyophilized LD-SLG-CS nanoparticles didn't show the peaks which were present in the of Levodopa and Selegiline hydrochloride.shown in figure 1(a, b & c).

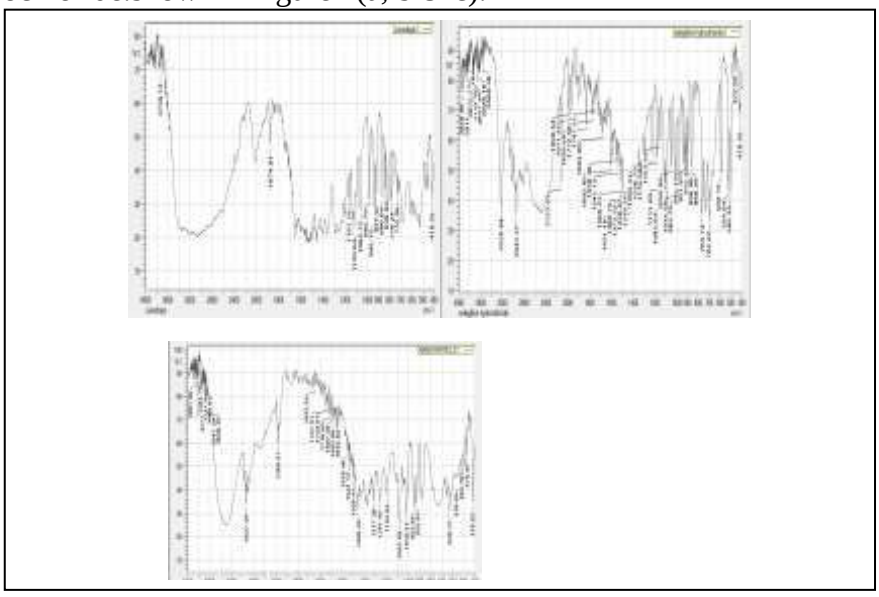


Figure 1: a) FT-IR spectrum of Levodopa: **b)** FT-IR spectrum of Selegiline Hydrochloride; **c)** FTIR Spectrum of Lyophilized LD-SLG-CS nanoparticles.

2. DSC Study:DSC thermogram of Levodopa and Selegiline hcl shows the single endothermic peaks at 283.35^{0}C and 143.94 ^{0}C respectively, corresponding to their melting points which confirmed that both drugs were pure. DSC thermogram of lyophilized nanoparticles were taken which gave the intense endothermic peak which is corresponding to the MP of the mannitol which was used for lyophilization.

3. Average particle size and Polydispersity Index:The formulation batch F8 showing average particle size. The results obtained in particle size, PDI and entrapment efficiency of batches are given in Table 1. The particle size of optimized batch is shown in figure 3.



Figure 3: Average Particle Size of optimized batch F8

Table 1: Average particle size, polydispersity index and entrapment efficiency of formulation batches with std deviation (SD)

Batch	Factor 1 A:Conc. of Chitosan %w/v	Factor 2 B:Conc. of TPP %w/v	Response 1 Particle Size±SD nm	Response 2 PDI±SD	Response 3 Zeta Potential±SD mV	Response 4 %EE of LD±SD %	Response 5 %EE of SLG±SD %
F1	0.25	0.4	207.9±1.20	0.420±0.023	30.2±1.6	62.88±2.31	31.4±2.36
F2	1	0.1	367.2±1.35	0.848±0.063	24.81±1.33	71.56±3.36	44.35±2.66
F3	0.5	0.2	102.1±2.02	0.368±0.012	26.45±1.64	85.19±2.56	51.32±4.29
F4	0.5	0.4	97.3±1.32	0.430±00.39	27.11±1.88	88.23±1.03	52.42±2.69
F5	1	0.4	343.2±1.75	0.615±0.054	24.43±2.03	81.46±1.65	46.88±2.57
F6	1	0.2	367.5±1.23	0.578±0.041	26.92±2.55	79.34±2.36	43.63±2.77
F7	0.25	0.2	191.4±0.96	0.393±0.055	32.94±1.96	66.99±2.68	27.45±2.88
F8	**0.5**	**0.1**	**112.9±1.30**	**0.353±0.013**	**28.18±2.58**	**94.03±3.02**	**58.01±1.97**
F9	0.25	0.1	155.7±2.6	0.383±0.038	29.37±2.94	56.66±2.09	24.48±2.65

4. Zeta Potential

Zeta potential of all batches estimated and it was found in the range of 23.81 to 31.20 mV and the optimized F8 batch having the zeta potential **28.18 ± 2.58** mV.optimized batch given below.

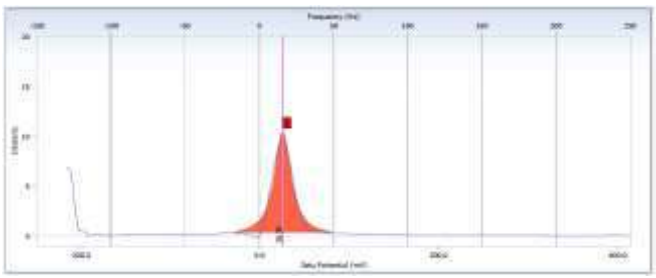


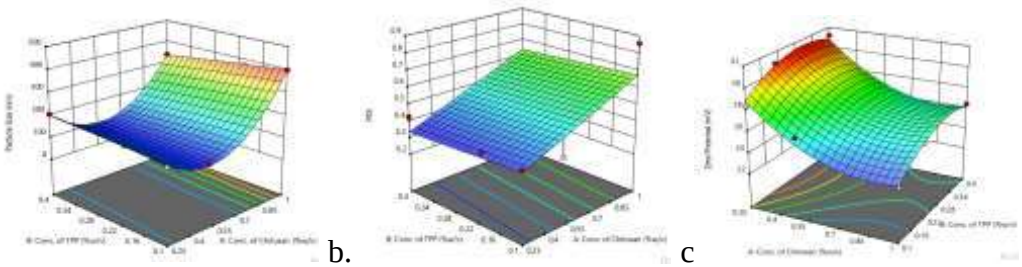
Figure 4: Zeta Potential of optimized batch F8

5. Percent Entrapment efficiency:

As showed in table 1. Batch F8 has highest entrapment for Levodopa and Selegiline HCl i.e. 95.03±3.02 and 58.01±1.97 respectively.

Response surface plot: 3 D response surface plots of factors vs responses were obtained from the Design of Expert software. As the concentration of chitosan increased from 0.25 % to 0.5 % the % entrapment efficiency of Levodopa and Selegiline HCl also increased. As the concentration of chitosan increased from 0.5% to 1% the % entrapment efficiency get reduced. By considering the all responses F8 is selected as optimum batch having particle size **112.9±1.30** nm, polydispersity index **0.350±0.013**, zeta potential **28.36±2.58** and % entrapment efficiency for Levodopa **94.03±3.02** and for selegiline HCl **58.01±1.97.**

a. b. c



d. e.

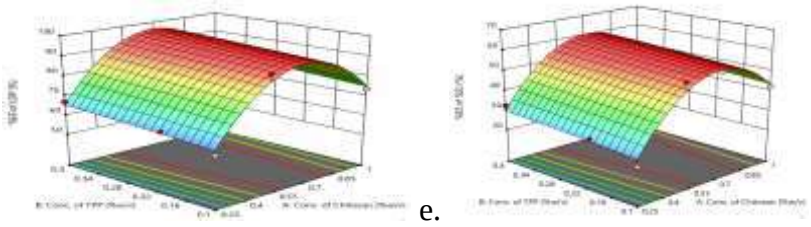


Figure 5: 3D Response surface plots of **a)** Particle size; **b)** PDI; **c)** Zeta potential **d)** % EE of Levodopa **e)** %EE of Selegiline HCl

6. Surface Morphology:

The SEM photomicrograph of LD-SLG-CS-NP is given in below figure 6 shows nanoparticles of dispersed size.

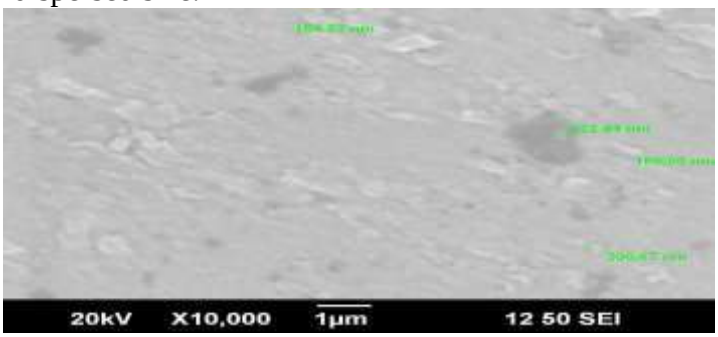


Figure 6: SEM photomicrograph of LD-SLG-CS-Nanoparticles

Characterization of *in-situ* nasal gel:

1. **Clarity:**The developed formulation was inspected visually for clarity against the white background and none particles seen in the sol as well as gel form of formulation.
2. **pH of gel:** pH of sol form of formulation was measured by using the calibrated pH meter pH was found to be 6.3 which were compatible with the nasal secretion and nasal mucosa.
3. **Gelation temperature:** The gelation temperature was found 30 ± 0.6 ^{0}C.
4. **Drug content estimation:** The drug content was estimated by using the standard calibration curve of both the drugs;

Table 2: Drug content estimation in nanoparticle loaded *in-situ* nasal gel

Sr. No.	Drug	Drug content in formulation
1.	Levodopa	92 ± 0.84 %
2.	Selegiline HCL	88±0.45 %

5. **Gel strength:** The gel strength of the gelled formulation was estimated and it found be 28 sec.
6. **Viscosity:** Viscosity of formulation in both forms i.e. in sol and gel form was estimated by Brookfield viscometer by using spindle no. 5.

Table 3: Viscosity of *in-situ* nasal gel

Viscosity of sol (cps)	Viscosity of gel (cps)
600 ±10.2	3000 ±60.53

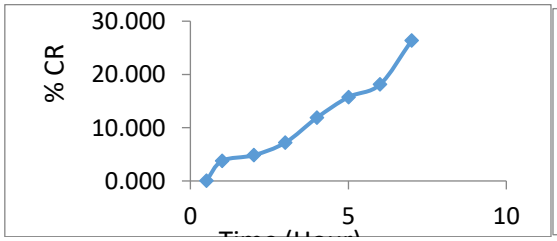
***7. In-Vitro* study:** *In-vitro* release profile of *in-situ* nasal gel was carried out for 8 hrs using Franz diffusion cell resembling the conditions of nasal mucosa at 37±0.5°C maintaining sink conditions. The % drug release is given in the Table 4 given below.

8. **Release Kinetic study:** Various release kinetics observed for both formulations. The release of Levodopa from plane *in-situ* nasal gel follows first order kinetics while in nanoparticle loaded *in-situ* nasal gel it follows Higuchi kinetics. The release of Selegiline HCl from plane *in-situ* nasal gel follows Higuchi kinetics while in nanoparticle loaded *in-situ* nasal gel it follows zero order kinetics.

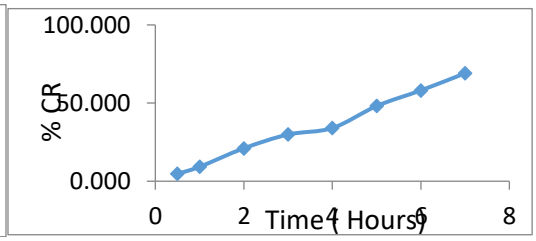
Table 4: *In-vitro* diffusion study of plane drug loaded in-*situ* nasal gel and nanoparticle loaded *in-situ* nasal gel

Sr. No.	Time in Hours	% Cumulative drug release (plane drug loaded in situ nasal gel)		% Cumulative drug release (nanoparticle loaded in-situ nasal gel)	
		LD	SLG HCl	LD	SLG
1	½	0.000	4.351	0.000	0.763
2	1	17.118	24.270	0.564	6.433
3	2	25.788	44.349	5.055	11.330
4	3	36.895	61.089	8.703	20.676
5	4	55.613	73.387	13.265	26.789
6	5	66.324	79.098	15.067	39.432
7	6	81.456	87.343	16.566	50.234
8	7	87.753	98.422	19.212	58.657

***Ex-Vivo* permeation study:** The *ex-vivo* drug LD-SLG-CS nanoparticle loaded in situ nasal gel was performed. The graphs plotted as Time vs % Cumulative drug Release (% CR). Levodopa showed that 28.229 % CR in 7 hours, while selegiline HCL showed 65.055 % CR in 7 hours.



a)



b)

Figure 8: *Ex-vivo* release kinetics of LDSLG-CS nanoparticle based *in-situ* nasal gel for: a) Levodopa b) Selegiline HCl

10. In vivo study: In vivo study of LD-SLG-CS nanoparticle based *in-situ* nasal gel was performed by using female wistar rats of average weight 200 grams. Locomotion activity (open field test), Grip strength and Akinesia test were performed on naive group, test group and disease controlled group.

a. Open field test:

In this test number of ambulations, grooming, wall climbing and rearing by animals were recorded and it was found that most of the parameters were significant.

Rat	No. of ambulations	Grooming	Wall climbing	Rearing
N1	36	31	06	05
N2	30	24	15	11
N3	26	26	04	03
H	20	27	09	02
B	22	29	07	00
T	18	21	04	00
U1	14	09	03	00
U2	07	15	01	00
U3	04	09	00	00

Table 5: Locomotion activity by open field test

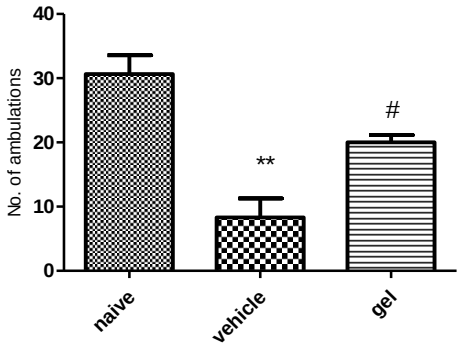


Figure 10: Graphical comparison between naive, vehicle and *in-situ* nasal gel treated rats for number of ambulation

**P<0.01 vehicle vs naive

# p< 0.05 vehicle vs gel

b. Grip strength and akinesia

Grip strength and akinesia test performed for all three groups and their values are given in below

Rat	Grip strength(sec.)	Akinesia
N1	60	44
N2	60	43
N3	60	58
H	40	39
B	48	30
T	53	23
U1	15	26
U2	28	27
U3	10	19

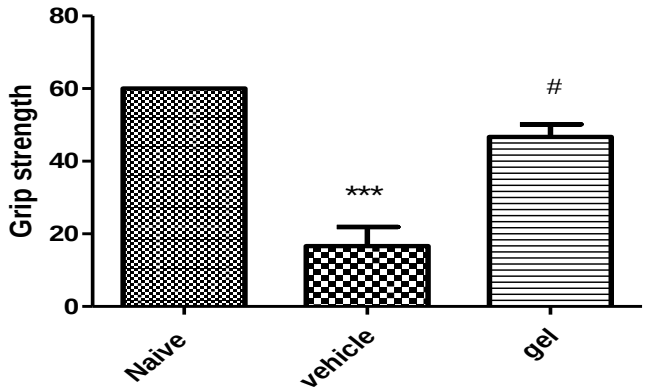


Table 6: Grip strength and Akinesia

fig.11: Graphical comparison between naïve,vehicle and *in-situ* nasal gel treated rats for grip strength

***p < 0.001 vehicle vs naive
# p < 0.01 gel vs vehicle

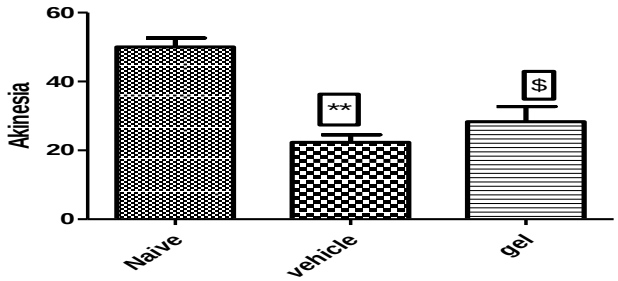


Figure 12: Graphical comparison between naive, vehicle and *in-situ* nasal gel treated rats for akinesia test.
** p< 0.01 vehicle vs naïve.
$ p>0.05 gel vs vehicle indicates non-significant difference between gel and vehicle treated animals. This is unexpected result for akinesia test ; reason behind this was unknown but might be due to the experimental conditions, laboratory conditions or any other unknown causes.

7. **Stability Study**

The LD-SLG-CS nanoparticle based in situ nasal gel was evaluated for stability studies stored in refrigerator at 5 ± 3 ^{o}C temperature for 3 month. The formulation shown good stability with no remarkable changes in viscosity, drug content, and gelation temperature which are shown in Table 7.

Table 7: Stability study testing

Sr. no.	Parameters		Storage period 3 months at 5 ± 3°C temp.			
			Initial	1 month	2 month	3 month
1	Viscosity (Cps)	sol	600 ± 10.2	700 ±12.05	650±14.23	626±14.09
		gel	3000 ±60.53	3213 ±45.12	3022±60.42	3043±12.03
2		LD	95±0.84	85.23±0.65	88.20±0.26	88.16±0.44

	Drug content (%)	SLG	86±0.45	82.78±0.82	82.12±0.53	82.03±023
3	Gelation Temp.		30 ± 0.6 ^{0}C	28.60 ±0.3^{0}C	28.90±0.4 ^{0}C	29.5±0.6 ^{0}C

Conclusion:

From the above study we can conclude that the Levodopa and selegiline combination may be the rational combination as no any evidence of their physical interaction were found also this combination omits the carbidopa as which is adjuvant in oral Levodopa therapy. Nanoparticles may reduce the dosing frequency. Ionotropic gelation technique is best suitable technique for the preparation of chitosan nanoparticles to deliver the antiparkinsonian drugs like Levodopa and Selegiline. As the gelation temperature of this formulation is 30 ^{0}C it will be suitable for human nasal administration and lowers the chances of drug wastage. Use of selegiline in combination with Levodopa prove beneficent.

101

Synthesis and characterization of 2-[2-amino-6-(3,4-substitutedphenyl)-6H-1,3-oxazin-4-yl]-4-chloro-3-substituted phenol with special reference to their antioxidant activity

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Abstract

A series of novel compounds, namely 2-[2-amino-6-(3,4-substitutedphenyl)-6H-1,3-oxazin-4-yl]-4-chloro-3-substituted phenol, were synthesized through the reaction of various chalcones as a precursors. The structures of these compounds were determined through elemental analysis and spectral techniques such as IR and 1H NMR spectroscopy. Subsequently, the synthesized compounds underwent biological evaluation.

A notable finding of the study was the discernible difference in antioxidant activity between the compounds featuring Cl and NH_2 substitutions within the 1,3-oxazin moiety, as assessed by the DPPH method. These results underscore the intrinsic variations in antioxidant properties associated with different substitutions within the 1,3-oxazin moiety. Furthermore, the study concluded that the substituted 1,3-oxazin moiety and its derivatives hold promise as potential sources of antioxidant activity.

Moreover, the presence of heteroatoms in these compounds was found to correlate with significant pharmacological activities, further highlighting the potential therapeutic relevance of this class of compounds.

Key words: Synthesis, characterization, 1,3-oxazin moiety, spectra, antioxidant activity.

Introduction

Heterocyclic compounds play a crucial role in the metabolism of all living cells. Among these compounds, oxazines have garnered interest over the past three decades but still lack extensive study. Oxazines are heterocyclic compounds comprising one nitrogen and one oxygen atom. Three isomers exist based on the relative positions of the heteroatoms and double bonds: 1,2-; 1,3-; and 1,4-oxazines. They represent an important class of heterocycles, drawing significant synthetic interest due to their diverse biological activities.

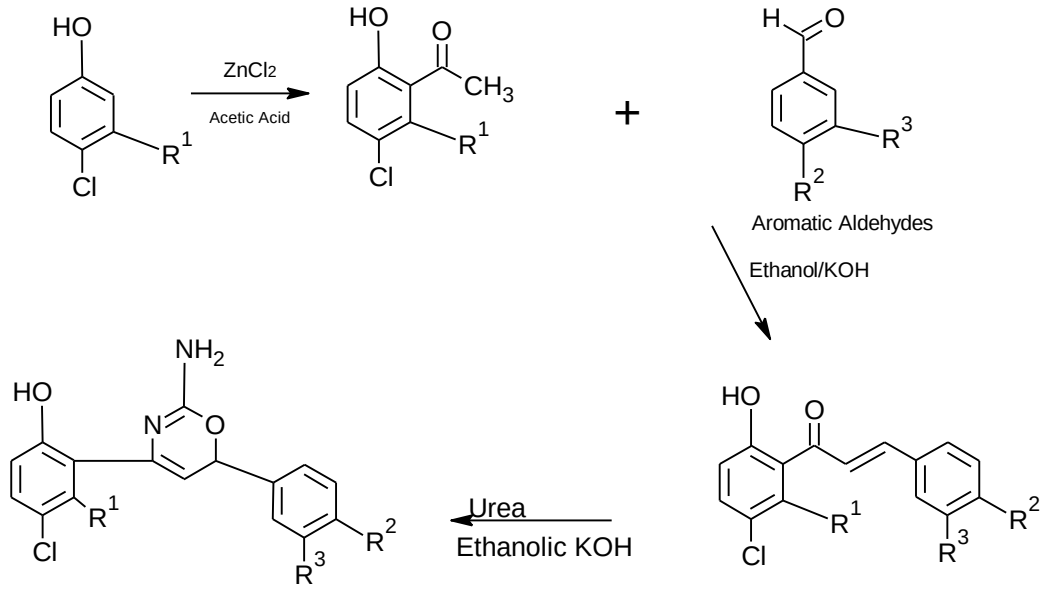
Oxazine heterocycles hold special significance as they form a vital class of both natural and synthetic products, exhibiting various biological activities. Their growing importance in pharmaceutical and biological fields motivates this review article, which aims to compile the synthesis methods of oxazine derivatives and their associated biological activities. These compounds find wide utility in organic chemistry synthesis due to their numerous synthetic applications hence it was thought to synthesize these compounds and study their antioxidant properties.

Materials and Methods :

A solution containing equimolar quantities of chalcones and urea dissolved in ethanolic potassium hydroxide was stirred for approximately 5-6 hours. Subsequently, the mixture was poured into a cold dilute hydrochloric acid solution and continuously stirred for an hour. The resulting mixture was refrigerated overnight, yielding a precipitate that was filtered and dried. The product was further purified through recrystallization using petroleum ethanol. The

structures of the synthesized compounds were determined through IR and H1 NMR analysis. The IR spectra displayed absorption bands consistent with anticipated values, while the H1 NMR spectra indicated the aromatic ring protons at their anticipated chemical shifts and integral values.

Scheme:



(3a – d)

Spectral Analysis of compound 3a:

IR : The IR spectra display the following principle absorption band Frequency (cm-1)
3298 -OH stretch 3245 -NH2 stretch 710 and 721 -C-Cl stretch 1575 -N-H stretch

NM R : The 1HNMR spectrum was noted in CDCl3 with TMS as an internal standard . The noticed chemical shifts can be correlated as fallows. Peaks observed in ppm
9.15 1H S –OH , 7.83 2H S -NH_2 , 6.55-7.37 7H M Ar-H , 5.25 2H S CH2 , 3.93 3H S -OCH3

Table1: Physical property of compounds

Compounds	R_1	R_2	R_3	Molecular Formula	MP◦C	%Yield	R.F. Value	% Nitrogen	
								Found	Calculated
3a	Cl	OCH_3	H	$C_{17}H_{14}N_2O_3Cl_2$	190	45	0.76	7.65	7.67
3b	Cl	OCH_3	OCH_3	$C_{18}H_{16}N_2O_4Cl_2$	183	49	0.68	7.08	7.09
3c	Br	OCH_3	H	$C_{17}H_{14}N_2O_3$ ClBr	199	56	0.62	6.82	6.84
3d	Br	OCH_3	OCH_3	$C_{18}H_{16}N_2O_4$ClBr	188	48	0.74	6.36	6.37

Antioxidant activities

7.1 Phenolic Contain

Total phenolic content was determined as described by Prior et al.. Briefly, 500 µg of compound in 100 µL of methanol was mixed with 100 µL of 1 N Folin–Ciocalteu reagent. Following incubation for 5 min, 200 µL of 20% Na_2CO_3 was added. Absorbance at 730 nm was measured in plate reader after 10 min and the concentration of phenolic compounds was calculated using standard curve of gallic acid (500–5000 ng; R^2=0.967). The results were

expressed as mg gallic acid equivalent (mg GAE) g^{-1} Total phenolic contain is obtained in molecule in 3a and 3c is 25.01 microgram GAE/mg and 7.9 microgram GAE/mg respectively

7.2 Flavanoid

For flav**a**noid content, extract in 500 µL of distilled water was mixed with 30 µL of a 5% $NaNO_2$solution and incubated for 5 min. 300 µL of 10% $AlCl_3.H_2O$ solution was added followed by 200 µL of 1 M NaOH and 200 µL of distilled water after 6 min. Absorbance was read at 510 nm and total flavonoids were calculated using quercetin as standard (10–100 µg; R2=0.999). The results were expressed as mg quercitin equivalent (mg GAE) g^{-1} Total flavanoid contain was found to be 57 microgram QER/mg and 59.27 microgram QER/mg in 3a and 3c respectively

7.3 DPPH Assay

1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay, hydroxyl radical ($OH^{\cdot}$) scavenging activity, reducing power assay and chelation power of compound 3a and 3b was performed with a few modifications for plate reader analysis. Reducing power of compounds **3a** and **3c** is obtained 69.72% and 59.31% respectively

Conclusion

A novel 2-[2-amino-6-(3,4-substitutedphenyl)-6H-1,3-oxazin-4-yl]-4-chloro-3-substituted phenol, were synthesized in good yield characterised by spectral and elemental analysis. compound 3a and 3c shows good antioxidant activity by DPPH assay.

Acknowledgement

The authors are thankful to the principal R.D. Deshmukh sir of RDIK and NKD College Badnera for providing necessary lab facility.

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102

Structural Characterization of Sulfur Nanoparticles Synthesized by Biowaste Orange Peels Extract via Herbal Method

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Abstract:
This research explores the eco-friendly synthesis of sulfur nanoparticles through a herbal method utilizing biowaste orange peels extract. The utilization of natural extracts for nanoparticle synthesis aligns with sustainable practices. The study focuses on optimizing the synthesis conditions and provides a detailed structural characterization of the resulting sulfur nanoparticles. Fourier Transform Infrared Spectroscopy (FTIR) is employed to analyze the crystalline structure and elemental composition. The findings contribute to the understanding of green synthesis methods and offer insights into potential applications in catalysis, sensors, and medicine. This research underscores the importance of sustainable approaches in nanomaterial synthesis using biowaste resources.
Keywords: sulfur nanoparticles, orange peels extract, etc

Introduction

Nanotechnology has emerged as a revolutionary field with profound implications across various scientific disciplines and industrial sectors. Among the plethora of nanomaterials, sulfur nanoparticles have garnered significant interest due to their unique properties and potential applications in fields such as catalysis, energy storage, and biomedicine. However, the methods employed for nanoparticle synthesis are often associated with environmental concerns and resource-intensive processes[1].

In the pursuit of sustainable and ecofriendly alternatives researchers are turning towards green synthesis methods that utilize natural resources and biowastes. Orange peels, a common agricultural byproduct rich in bioactive compounds, present an intriguing source for nanoparticle synthesis. This research delves into the synthesis of sulfur nanoparticles via a herbal method using biowaste orange peels extract. The integration of herbal techniques not only aligns with the principles of green chemistry but also offers a cost-effective and scalable approach for nanoparticle production[2].

The overarching objective of this study is to investigate the structural characteristics of sulfur nanoparticles synthesized through this innovative method. Understanding the morphology, crystalline structure, and surface properties of these nanoparticles is crucial for unlocking their full potential in diverse applications[3]. By focusing on the structural characterization, this research aims to contribute to the growing body of knowledge on green synthesis methods and advance the understanding of sulfur nanoparticles as a promising nanomaterial.[5] This introduction sets the stage for exploring the synthesis of sulfur nanoparticles using via a herbal method and emphasizes the significance of structural characterization in unlocking the full potential of these nanoparticles in various applications[4].

The objective of this research is to explore the feasibility of phytofabricating sulphur nanoparticles using biowaste orange peels extract and to characterize their structural properties.

The characterization techniques, including X-ray diffraction (XRD) and Fourier Transform Infrared Spectroscopy (FTIR, will be employed to gain insights into the crystalline structure, morphology, surface functionalization, and optical properties of the synthesized sulphur nanoparticles[6-7].

EXPERIMENTAL SECTION:

The synthesis and characterization of sulphur nanoparticles phytofabricated via green synthesis using orange peels extract involve a series of experimental techniques. The following outlines the key methods employed in this study.

1. Collection and Preparation of orange peels **Extract:**

- Waste orange peels are collected from fruit juice center of local market of Chandur Bazar and thoroughly washed to remove impurities.
- The peels are finely chopped or ground to increase the surface area for efficient extraction.
- The peels extract is obtained by heating the crushed peels material with water and filtering the resulting solution as orange peels extract.

2. Green Synthesis of Sulphur Nanoparticles:

- Sulphur nanoparticle synthesis is initiated by combining the orange peels extract with sodium thiosulphate as sulphur precursor
- The reaction mixture is then subjected to heating for 2 hours to facilitate the formation of sulphur nanoparticles by the bioactive compounds present in the orange peels extract.
- The synthesis process is closely monitored to ensure the desired nanoparticle formation.

3. Structural Characterisation of Synthesized SNPs:

- The synthesized SNP sample is subjected to FTIR spectroscopy to analyze the functional groups and biomolecules involved in the stabilization and capping of the sulphur nanoparticles.

RESULT AND DISCUSSION

Fourier Transform Infrared spectroscopy (FTIR)

FTIR spectra of nanosulphur particles synthesized by using orange peel extract is given below

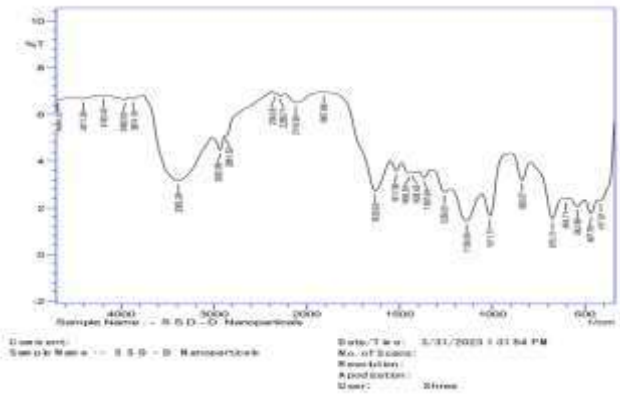


FIG: FTIR spectra of SNPs synthesized by using Orange peel extract

In the present study FTIR Spectra of SNPs synthesized by using orange peels shows characteristic bands at 3383.29, 1629.92, indicates characteristic bands of O-H and N-H groups, band at 1629.92 indicates carboxylic groups of orange peels shifted to low frequency region. While the bands at 1138.05, 1011.71 cm-1 are due to CO stretching of peel extract. The FTIR spectrum of synthesized sulphur nanoparticles shows all characteristic peaks of S-S stretching frequencies over the range 675.11- 417.61 cm-1.

FTIR spectra of SNPs shows a new linkage of sulphur nanoparticles in which orange peels extract can bind to sulphur nanoparticles through C=O, N-H, O-H linkages present in amino acid residues of extracts. Thus these can act as stabilizer surfactant and dispersing or

capping agent for synthesized sulphur nanoparticles and prevent agglomeration of sulphur nanoparticles.

CONCLUSION:

In this study, a novel, simple cost effective and environmentally benign synthesis method for the preparation of sulfur nanoparticles from sodium thiosulphate in the presence orange peel extract was developed. The biomolecules and phytochemicals present in the orange peels not only reduce the sulphur ions and also stabilize the sulphur NPs. The synthesized SNPs were characterized by FT-IR spectroscopic technique. The obtained results showed that as prepared monoclinic SNPs. The explored ecofriendly, high efficient SNPs synthesized using orange fruit peel extract are expected to have more extensive applications in biomedical and agricultural fields.

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103

Thermal Decomposition Kinetics of Cr(III), Mn(III), Fe(III), VO(IV) and UO_2(VI) Schiff Base complexes

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Abstract:
The thermal behaviour of Cr(III), Mn(III), Fe(III), VO(IV) and UO_2 complexes derived from Schiff base derived from thiocarbohydrazide was studied by thermogravimetric analysis(TG). The thermogravimetric analysis for complexes suggests the absence of water molecule in or out of the coordination sphere. From the change in weight with respect to temperature, activation energy, free energy and order of reaction of complexes was calculated. The spectroscopic data pointed out the behaviour of the ligand towards metal ions from which the coordination number of complexes exhibited to be five and six. The activation energy, free energy and order of reaction of complexes were calculated using Broido and Horowitz-Metzger methods.
Keywords: Thiocarbohydrazone, Metal complexes, Thermal decomposition.

INTRODUCTION

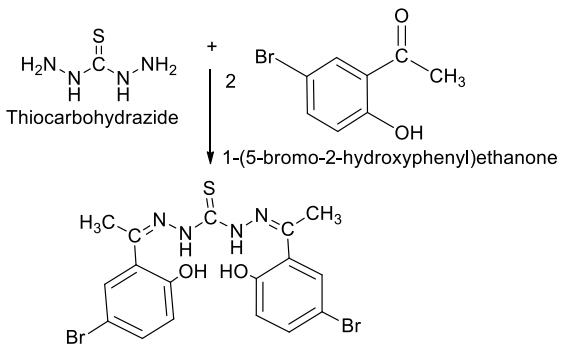
The coordination chemistry of complexes of thoicarbohydrazone ligand is a fascinating area, which has attracted the attention of inorganic chemists [1]. Over the past few years, physicochemical and chemotherapeutic properties of acyclic Schiff base complexes derived from thiocarbohydrazone ligands have become progressively more significant. The additional hydrazine moiety in thiocarbohydrazide results the ligand of significant metal-bonding modes, structural diversities and promising biological implications [2]. Metal complexes of ligand containing ONS donors have antibacterial [3], anticancer [4], antifungal [5] and antitumor activity [6] wherefore it is highly prudent to synthesize and characterize Schiff base metal complexes derived from thiocarbohydrazone. The present work is dealing with the thermal study of Cr(III), Mn(III), Fe(III), VO(IV) and UO (VI) metal complexes with the ligand derived from thiocarbohydrazide and 5-bromo-2-hydroxyacetophenone in 1:1 metal to ligand ratio [7]. The thermal parameters were calculated using Broido [8] and Horowitz-Metzger [9-10] methods. The complexes are thermally stable and their thermal decompositions are multistage processes. The complexes are subjected to a TG analysis from 50-850°C.

MATERIAL AND METHODS

All the chemicals used as a starting material for the synthesis of the ligand and their metal complexes were of AR grade or chemically pure, solvents were purified and dried before use. The metal complexes were prepared by mixing the ethanolic solution of metal salt with the solution of ligand by setting the suitable reaction conditions. Thermal analysis results of the complexes were obtained at a rate of 10^0C per minute on a Rijaku-Thermo plus EVO2 thermodilatometer.

Synthesis of the Schiff base ligand:

Thiocarbohydrazide and 5-bromo-2-hydroxyacetophenone were prepared by reported methods [10-11]. The mixture of thiocarbohydrazide (0.01mole, 0.91g) and 5-bromo-2-hydroxyacetophenone (0.02mol, 4.30g) in absolute ethanol (20 mL) was refluxed for 2 h (Scheme 1). The reaction mixture then allowed for cooling to room temperature for half an hour. A yellow precipitate was formed, which was filtered, washed with cold distilled water, and dried under vacuum. (yield 73%).



Scheme 1: Synthesis of the Schiff base ligand.

Synthesis of Cr(III), Mn(III), Fe(III), VO(IV) and UO_2 Complexes:

Equimolar quantities of respective metal salt and the ligand were dissolved separately in absolute ethanol (30 ml). Both the solutions were filtered and mixed in hot condition. The reaction mixture was refluxed for 5 hrs in a water bath. The colored products obtained were filtered, washed several times with hot water followed by ethanol and diethyl ether.

RESULTS AND DISCUSSION

Thermogravimetric analysis of the complexes:

Thermal decomposition of metal complexes is an important study as it provides useful information about the thermal stability of complexes as well as the coordination ability of water whether it is inside the coordination sphere or outside. The half decomposition temperature, Entropy Change (ΔS), Free Energy Change (ΔF) and Frequency Factor (Z) of compounds were calculated by employing Broido and Horowitz-Metzger [12]. The thermal curves of ligand and complexes were obtained with heating rate 10^0 C min^{-1} are given in fig. 1, while the kinetic parameters are assigned in Table 1. The ligand shows two-step decomposition pattern with the lowest half decomposition temperature. The Cr(III), Fe(III) VO(IV), and UO_2(VI) complexes indicate a two-stage decomposition pattern whereas Mn(III) complex shows a three-stage decomposition pattern. The UO_2(VI) complex shows the elimination of one lattice water molecules while Mn(III) and Fe(III) complexes show the elimination of two lattice water molecules respectively up to 120^0C indicates the presence of non-coordinated water molecules in the complexes. On the other hand, Cr(III) and Fe(III) complexes exhibit loss of one water molecule between 120- 220^0C which indicates the presence of coordinated water molecules in the complexes. [% wt. loss, obs./ calcd.] Mn(III):5.59/5.80; Fe(III):5.94/5.59 and UO_2(VI):2.17/2.28 for lattice water and Cr(III):2.70/2.98; Fe(III):8.57/8.39 for coordinated water. In the TG curve of VO(IV) complex, no weight loss up to 220^0C indicates the absence of any water molecule in the complex. Further weight loss was observed above 440°C, which may be due to the thermal degradation of the free part of the ligand along with some other side chain present in the complexes. A gradual weight loss observed above 440^0C, due to the degradation of the actual coordination part of the ligand and TG curves attain a horizontal level above 580^0C suggesting the formation respective stable metal oxides. From the half decomposition temperature, the relative thermal stability of the compounds is found to be UO_2(VI) > VO(IV) > Mn(III) > Cr(III) > Fe(III) > LH_2.

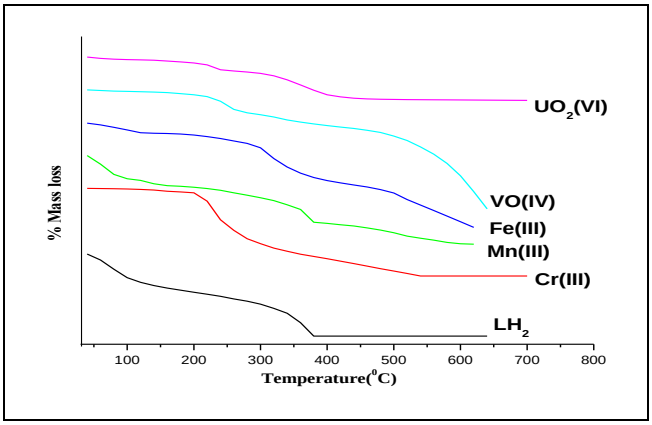


Figure 1 : Thermal degradation of ligand and its metal complexes.

Table 1 Thermal decomposition data of compounds.

Compound	Half Decomposition Temp (^{0}C)	Ea (kj/mole^{-1})		Entropy change ΔS (J/mol/K)	ΔF (kJ/mol)	Frequency factor Z (S^{-1})	Apparent entropy change S* (kJ)	Order of Reaction (n)
		BR*	H-M**					
LH_2	160	11.12	11.05	-347	121	165	-22.64	0.96
[Cr(L) Cl (H_2O)]	425	25.36	24.98	-214	95	159	-27.72	0.91
[Mn(L) OAc].2H_2O	440	13.26	13.85	-275	97	185	-22.67	0.92
[Fe(L)Cl(H_2O)].2H_2O	390	18.22	18.64	-267	85	141	-22.49	0.99
[VO(L)]	465	21.84	22.04	-327	102	136	-22.30	0.95
[UO_2(L)].H_2O	480	16.17	16.63	-319	95	174	-26.11	0.97

CONCLUSION

The activation energy calculated by the Broido and Horowitz- Metzger methods are in good agreement with each other. Thermodynamic parameters have been calculated on the basis of thermal activation energy and values are given in Table 1. The thermal stability of the compounds can be correlated with the substituent group attached to the ligands. It is found that more substituted ligands may have more thermal stability than more substituted ligands.

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104

A Comparative Analysis of Molecular Docking: Mono Versus Bis Derivatives of Isoniazid

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Abstract:
With rising resistance to isoniazid in tuberculosis treatment, we explored novel formulations by doing molecular docking studies with the crucial anti-tuberculosis protein 1ZID. We compared the binding affinities of mono and bis derivatives of isoniazid designed by combining with mono and dialdehydes, respectively. Our results revealed that dialdehyde combinations exhibited significantly stronger binding energies, suggesting enhanced interaction with the 1ZID protein. Our findings underscore the promise of these formulations, particularly those with dialdehydes, as future anti-tuberculosis therapeutics, urging further experimental validation for clinical translation and combating drug-resistant tuberculosis.
Keywords: Isoniazid, Molecular docking, Tuberculosis, etc.

Introduction:

The bacteria Mycobacterium tuberculosis (Mtb) is the organism that causes tuberculosis (TB), a very serious infectious disease. As the second most common infectious illness to cause death globally, tuberculosis (TB) continues to be a major health concern[1]. For the treatment of tuberculosis the medicinally significant drug isoniazid (INH) was first identified in 1950 [2]. Medication resistance has become more difficult to treat due to patient noncompliance with treatment regimens and organismal gene mutation, hence the development of novel INH derivatives is desperately needed to tackle it[3]. Derivatives of hydrazone are very effective in combating mycobacterial resistance. It can be utilised as a less costly substitute for isoniazid. Stable hydrazones are produced when isoniazid is mixed with specific hydroxy aldehydes; these compounds increase biological activity, reduce toxicity, and inactivate the isoniazid NH_2 group[4]. Hydrazone is one of the biologically important Schiff bases[5]. In hydrazoneazomethine linkage is present. The azomethine class of chemicals is crucial for the creation ofnovel pharmaceuticals[6]. Hydrazones are a promising precursor for bioactive heterocycles since they belong to the azomethine group in the hydrazone chemical family. Hydrazone compounds play a significant role in coordination chemistry, medicine, and cosmetics. Hydrazones are used as DNA-binding agents in genomic and medical research, as well as diagnostic tools, because of their diverse biological characteristics. The atoms of carbon and nitrogen in hydrazone significantly affect its chemical characteristics. Because of its unique features, hydrazones have attracted the attention of pharmaceutical and medical chemists[7]. Hydrazone is significant since it contains compounds with a range of biological functions. Because the NH_2 group is inhibited, some synthetic hydrazide-hydrazones have been demonstrated to be less hazardous than hydrazides. These findings increase the hydrazide- hydrazone chemical synthesis's growing significance[8]. In order to create effective therapies,molecular docking is essential for drug development since it predicts how tiny compounds will interact with proteins. It revolutionises pharmaceutical research and facilitates targeted drug design by helping to comprehend molecular interactions at the atomic level, optimising drug candidates, and speeding up the development of novel treatments. Thus, adding the hydrazonemoiety to the structure of approved antimycobacterial drugs like

isoniazid as well as new drugcandidates is a sensible and widely employed method to produce innovative antitubercular compounds with lower toxicity[9].

Experimental:

Molecular docking stands as a crucial computational technique in molecular biology and bioinformatics, enabling the prediction of a ligand's binding mode and affinity to a target protein. In this paper, we utilized PyRx (Python Prescription), a user-friendly graphical interface for AutoDock Vina, a widely used molecular docking software. The following stepwise procedure guided our docking experiments.

The initial step involved the installation of PyRx, necessitating a pre-existing setup of Python. PyRx could be downloaded from its official website, streamlining the integration of AutoDock Vina into our workflow. With the software in place, our subsequent steps focused on preparing the necessary input files. For the target protein's 3D structure, we accessed databases like the Protein Data Bank (PDB), ensuring compatibility with PyRx. Simultaneously, the ligand's 3Dstructure was prepared in various formats (e.g., PDB, MOL2, SDF) using tools such as Open Babel, facilitating the subsequent docking simulations.

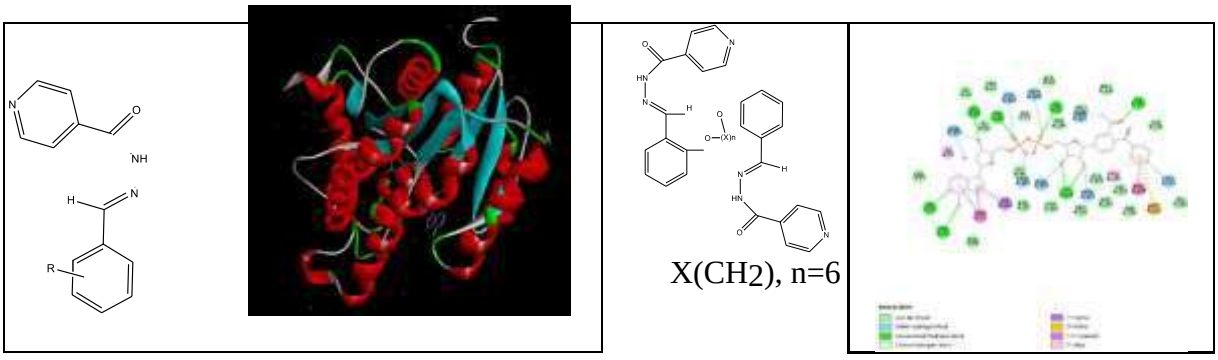
Upon setting up a new project in PyRx, we imported both the protein and ligand structures. Crucial to the success of our experiments was the careful configuration of docking parameters. The definition of the search space, exhaustiveness, and other relevant settings played a pivotal role in the accuracy of our predictions. Subsequently, the docking simulation was initiated using the AutoDock Vina engine embedded within PyRx. Throughout this phase, constant monitoring ensured the successful completion of the simulation.

Post-simulation, our focus shifted to result analysis. The docking results provided insights into the ligand's predicted binding pose and affinity. PyRx's built-in molecular visualization tools facilitated a comprehensive examination of the binding interactions.

Results & Discussion:

Table 1: Binding affinity of ligand protein interaction

Sr. No.	1	2	3	4	5	6
Ligand	IHA	IHBA2	IHBA3	IHBA4	IHBA5	IHBA6
Binding Energy	-8.6	-14.5	-14.6	-14.9	-15.2	-15.6



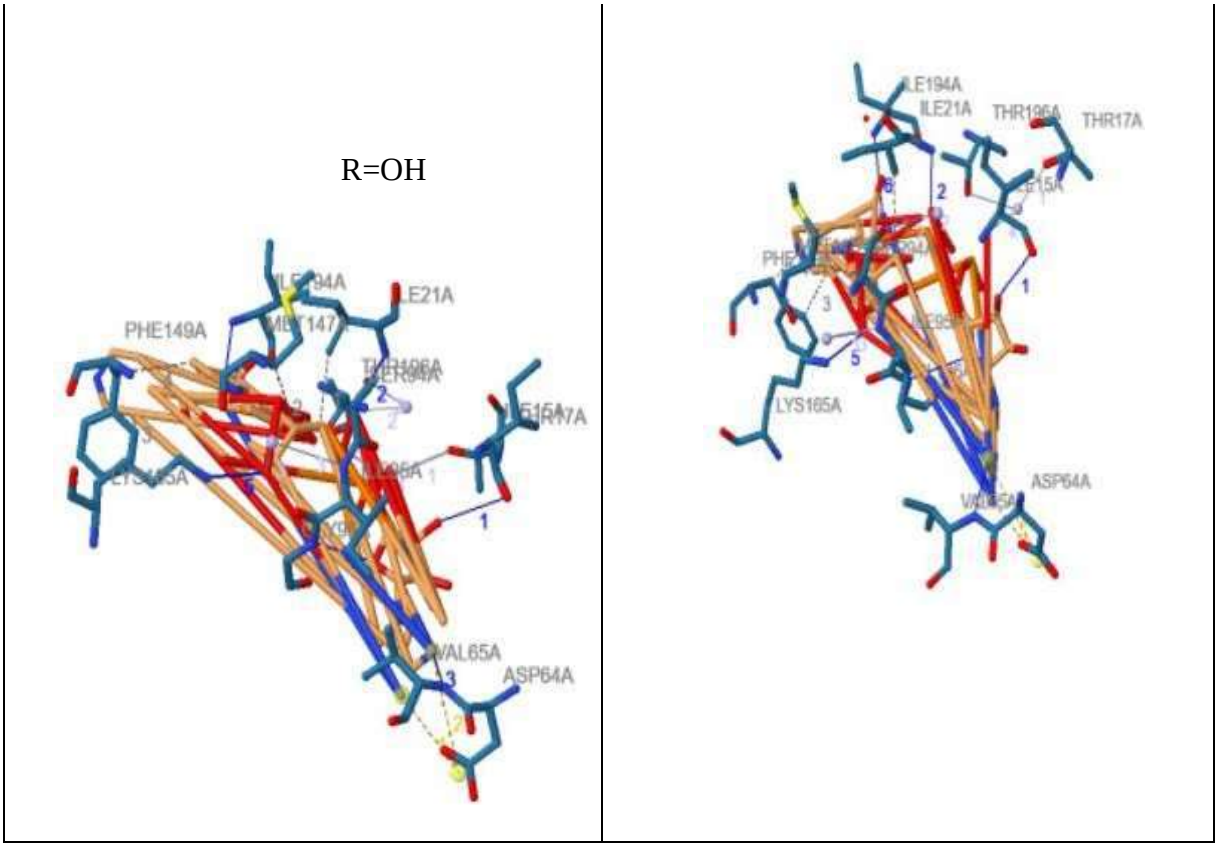


Fig: Molecular docking showing the interaction of 1ZID protein with Ligand

Our study underscored the designing of Isoniazid derivatives particularly bis-hydrazones andthe ligand-protein interaction. Molecular docking study utilizing PyRx software and the 1ZIDProtein from the Protein Data Bank, reveals, Bis hydrazones of isoniazid demonstrated significantly higher binding affinity compared to mono derivatives, these observation of elevated binding energies highlights the enhanced efficacy of bis hydrazones. It's also observed
that, in the case of bis hydrazones as the length of linker chain increases binding affinity increases. Six carbon chain linker shows high binding affinity than others. These findings suggest a promising avenue for the development of isoniazid derivatives, emphasizing the potential of bis hydrazones as superior candidates for further exploration and drug developmentefforts against tuberculosis, particularly in cases where mono derivatives may exhibit diminished effectiveness.

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105

Eco-Friendly Synthesis and Characterizaton New Chalcone Derivatives

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ABSTRACT:
The presented chalcone were synthesized from 2-hydroxy-5-methyl acetophenone and different chloro- substituted aldehydes. All the chalcones were characterized trough IR, PMR and elemental analysis. Magnetic stirring technique is used to follow the green synthesis way for the synthesis of chalcone.

Key words: Chalcone, Green synthesis and Spectral studies.

INTRODUCTION:

Chalcones, α, β-unsaturated carbonyls, play a crucial role in many biological processes as well as are well-known intermediates for synthesizing various heterocycles and bear a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed. Presence of enone functionality in chalcone shows the antibiotic activity. There are many molecules containing ring such as imidazole, triazole, pyrazole, benzimidazole, benzotriazole, oxypurine, pyrimidinyl, naphtyl, 1, 3-dioxolane, thiosemicarbazone, pyridine, furan, thiophene which have shown antibacterial activity,,,. Pyrazolines and Isoxazolines have usually been synthesized by starting from aldehydes or ketones, which have either actual or potential α,β-unsaturation with substituted hydrazine under reflux condition in the presence of base , , .

2. MATERIALS AND METHODS

Starting materials and solvents used for each reaction is of synthetic grade procured from S D Fine, and the products obtained were assessed for purity by physical constant determination, and Thin Layer Chromatography (TLC).

All the reactions were monitored using thin layer chromatography on pre- coated TLC plates (Silica gel 60-120#) using solvent system Benzene: Ethanol [8:2] for series-1 compounds and Dichloromethane: Ethyl acetate [9:1] for series-2 compounds. TLC was performed by ascending development in a chamber previously saturated with the solvent system. TLC plates were observed under long UV lamp in UV chamber for detection of spots. The synthesized compounds were purified by recrystallization and their structures were characterized by Physical constant, IR and NMR. They have shown single spot-on TLC plate when observed under UV light; Melting points were taken in open capillaries on melting point apparatus and were uncorrected. The Infra-red Fourier-transform infrared (IR) spectra were recorded as KBr pellets using Perkin- Elmer spectrometer. PMR spectra were recorded on BRUKER AVANCE NEO 500MHz NMR spectrometer in CDCl3 solvent.

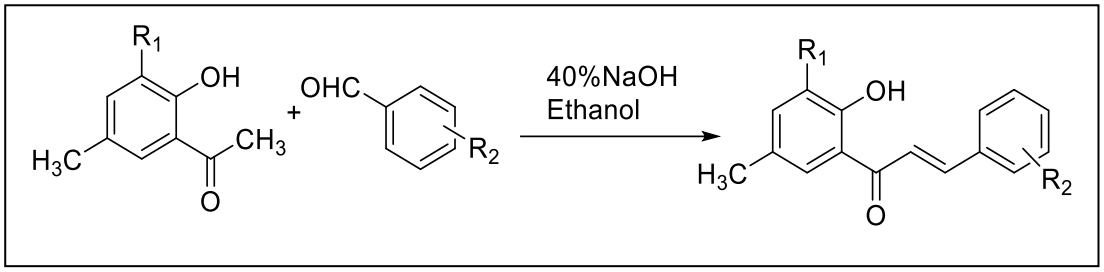
Claisen-Schmidt condensation reaction was used for synthesis of chalcones, . The eco-friendly procedure used was optimized and is given below.

We have previously synthesized 2-hydroxy-5-methyl acetophenone (2) 2-hydroxy-3-nitro-5-methyl acetophenone (3). In a recently published paper, we discussed synthesis snd antimicrobial studies of newly synthesized 3-(substituted)-1-(2-hydroxy-5-methyl-3-nitro phenyl) prop-2-en-1-ones. The consistent study of the eco-friendly synthesis and characterization new chalcone derivatives contain Indol and Piconaldehyde moiety.

Synthesis of chalcone derivatives:

2-hydroxy-5-methyl acetophenone (2)/ 2-hydroxy-3-nitro-5-methyl acetophenone (3) (0.01mol) was dissolved in suitable solvent and aromatic heterocyclic aldehyde (0.01mol) was added with constant stirring at room temperature. Then NaOH solution was added to reaction mixture which was stirred for 24 hrs at room temperature. Finally, the reaction mixture was poured into crushed ice and neutralized with HCl. The product separated out, was filtered, washed with water, dried, and recrystallized from alcohol to give chalcone. All products satisfy the 1 H NMR spectroscopic data. M.P. and % yields of products 5a-g are given in Table 1. The name of synthesized chalcones entitled below.

- 1-(2-hydroxy-5-methylphenyl)-3-(1H-indol-3-yl) prop-2-en-1-one (4a)
- 1-(2-hydroxy-5-methylphenyl)-3-(pyridin-2-yl) prop-2-en-1-one (4b)
- 1-(2-hydroxy-5-methyl-3-nitrophenyl)-3-(1H-indol-3-yl) prop-2-en-1-one (5a)
- 1-(2-hydroxy-5-methyl-3-nitrophenyl)-3-(pyridin-2-yl) prop-2-en-1-one (5b)



R_1 = H, NO_2 and R_2 = Indol-3-carboxy aldehyde and Piconaldehyde

Schematic procedure for synthesis of chalcone derivatives

Table 2: Physical data of synthesized compounds (4a and 4b, 5a and 5b)

R_1	R_2	Product	M.P.	%Yield
H	Indol-3-carboxy aldehyde	4a	128^0C	84%
H	Piconaldehyde	4b	117^0C	64%
NO_2	Indol-3-carboxy aldehyde	5a	138^0C	88%
NO_2	Piconaldehyde	5b	124^0C	74%

Result and Discussion:

The condensation of substituted acetophenone2 and 3 with substituted aldehydes in ethanolic alkali yielded substituted chalcones which were purified by recrystallization in ethanol. All products were characterized by IR and proton NMR spectroscopy.

1-(2-hydroxy-5-methylphenyl)-3-(1H-indol-3-yl) prop-2-en-1-one (4a)

IR data: - 3450 - O-H stretch, 3180- -N-H stretch Indol, 3110- -C-H stretch aromatic, 2910 -C-H stretch aliphatic, 1620- -C=C, 1705-C=O stretch, 1250- -C-O stretch, 1446- -C=C stretch;

^{1}H NMR (DMSO, delta ppm):- 8.6(d, 1H), 8.4(d, 1H), 7.8 (s, 1H), 7.6 (m, 4H), 5.8 (d,1H) , 4.7 (S, 1H), 2.6 (S, 1H), 2.5 (s, 3H).

1-(2-hydroxy-5-methylphenyl)-3-(pyridin-2-yl) prop-2-en-1-one (4b)

IR data: - 3450 - O-H stretch, 3110- -C-H stretch aromatic, 2910 -C-H stretch aliphatic, 1620- -C=C, 1700-C=O stretch,1250- -C-O stretch, 1446- -C=C stretch;

^{1}H NMR (DMSO, delta ppm):- 8.5(d, 1H), 8.3(d, 1H), 7.7 (s, 1H), 8.6 (m, 4H), 5.6 (d,1H) , 4.7 (S, 1H), 2.4 (s, 3H).

1-(2-hydroxy-5-methyl-3-nitrophenyl)-3-(1H-indol-3-yl) prop-2-en-1-one (5a)
IR data:- 3743 - O-H stretch, 3169- -N-H stretch indol, 3049- -C-H stretch aromatic, 2931 -C-H stretch aliphatic, 1631- -C=C-C=O stretch, 1525- $-NO_2$ (asymmetric) stretch, 1342- $-NO_2$ (symmetric) stretch, 1134- -C-O stretch, 1446- -C=C stretch; **^{1}H NMR (DMSO, delta ppm):-** 8.8(s, 1H), 1.5 (s, 3H), 7.8 (s, 1H), 7.3 (m, 4H).

1-(2-hydroxy-5-methyl-3-nitrophenyl)-3-(pyridin-2-yl) prop-2-en-1-one (**5b**)
IR data: - 3450 - O-H stretch, 3110- -C-H stretch aromatic, 2910 -C-H stretch aliphatic, 1620- -C=C, 1700-C=O stretch,1250- -C-O stretch, 1446- -C=C stretch 1525- $-NO_2$ (asymmetric) stretch, 1342- $-NO_2$ (symmetric) stretch, 1134- -C-O stretch, 1446- -C=C stretch;
^{1}H NMR (DMSO, delta ppm):- 8.7(s, 1H), 8.4(s 1H), 8.6 (m, 4H), 5.5 (d,1H) , 4.6 (S, 1H), 2.4 (s, 3H).

CONCLUSION

In conclusion, we have synthesized a number of various Chalcone derivative (4a-4b and 5a-5b). The reaction conditions were established and found to be reproducible. These derivatives may exhibit various pharmacological activities as indicated by PASS.13

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106

Synthesis and Application of Sorbitol Based polymers and their cleaning capacity

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Abstract:
For several thousands of years natural polymers have been indispensable for mankind to serve as food, to provide shelter and clothing and to serve as a source of energy. During the development of the human society the use of natural polymers become more sophisticated illustrated by the development of various technologies such as papermaking, textile manufacturing and wood processing. In mid nineteenth century the chemical modification of natural materials gave rise to the first commercial thermoplastic materials like cellulose acetate and nitrate and vulcanized natural rubber. But now days these synthetic polymers [are] present in almost every aspect in our life. In this race, synthetic natural products based polymers and their applied products are being increasingly explored because of their potential applications. The present work is aimed at developing a polymeric surfactant based on sorbitol, maleic anhydride and phthalic anhydride. As the polymeric surfactant is based on sorbitol and sugar it will have certainly biodegradability characteristics. And it is used in the detergent powder formulation a partial substitute for LABS.
Key words: Polymer, surfactants, detergents

Synthesis of Sorbitol based polymer

The synthesis of desired polymers[1] has been carried out in a round bottom glass flask of 1 litter capacity. A condenser is attached to it. Exactly weighed quantities of various ingredients were introduced into the flask. There after the heating was commenced slowly and steadily to attain the temperature of 120-130^{0}C in about 90 minutes in an electric heating mantle with temperature controlling regulator. Heating was continued for three hours and then the total reactor mass was cooled to 80^{0}C. The prepared polymer samples were then stored in tightly corked bottles. These polymer samples were systematically analysed for their acid value, viscosity, H.L.B. and pH by standard laboratory methods.

Preparation of powder detergent

Composition of various ingredients used in the preparation of detergent powder are shown in the formulation table. The said ingredients in the powdered form are weighed and mixed thoroughly in a tray. Then the liquid ingredients like acid slurry, sodium lauryl ether sulphate (S.L.E.S), and polymer were added. This mass then homogenized thoroughly in a homogenizer pot and then homogeneous mass thus obtained was packed in plastic pouches.

The surface tension of powder detergents solution was measured using stalagmometer (for 1%, 0.5% and 0.25% concentrations). Foam was measured by using mechanical agitation in a closed glass cylinder of 1L capacity.

Analysis and testing of powder detergent

Stain preparation

The soil medium having following composition by weight, Carbon black (28.4%), coconut oil (35.8%), Lauric acid (17.9%), Mineral oil (17.9%) was prepared. The mixture of carbon black and lauric acid along with mineral oil was taken in a pastel mortar. Coconut oil was then added slowly to form a thick paste. All the components were ground in the pastel mortar for 1-2 hours till a finely grounded mixture was obtained. The fine grinding is indicated by smooth feel of the paste medium. Soil solution was prepared by adding 2 g of above soil

medium paste in 500ml of carbon tetrachloride for staining cloth sample. The solution after preparation was kept in packed bottles.

Tea stain solution

This was prepared with following composition. Tea (TajMahal) (2.2%), sugar (8.0 %) , milk and water. Water was warmed to 35 to 40^{0}C and tea powder and sugar were added to it. The contents were further warmed till the solution starts boiling and at this stage milk was added and heating was continued at boiling temperature of the mixture for further 5 minutes. The prepared tea was passed through a tea filter and was used as tea medium for staining the clothes.

Preparation of Coffee medium

This was prepared with composition of coffee (1%), sugar (8.1%), milk (51.9%), water(39%), 25g of milk and water were taken in a beaker and the contents were warmed initially to a temperature of 35- 45^{0}C before adding the coffee powder and sugar. The heating was continued and the mixture was allowed to boil for about 5 minutes. The prepared coffee was passed through a coffee filter and was used as coffee medium for staining the clothes.

Method of application of Soil:

The cloth pieces of size 24×32 cm^2 were prepared. 50 ml of soil solution was taken in a beaker and the cloth sample was dipped in it for 5 minute. Thereafter the cloth piece was kept outside for drying in open atmosphere for 2 hours. After drying the cloth was cut into small size of 6×8 cm samples which were then used for washing.

Method of application of Tea and Coffee and oil stains

The stains of tea and coffee mediums were applied at the centre of cloth samples of 6×8 cm^2 size by using pipette. The stain applied was distinctly visible. The cloth sample was then kept in an oven at 55-60^{0}C for about 15 min and used for testing.

Method of Washing

The solutions of different concentration of detergent powder (1%, 0.5% and 0.25%) were prepared. Heat these solutions to temperature of 60^{0}C. Dip soiled cloth sample in it for 5 minutes and give to and for 10 hand washes. Allow it to dry and visualized the effect on stain.

Results and Discussion

Table-1 gives composition of various polymers designed specifically for use in detergents. The main common feature of all polymers[1] is the use of 90 % eco-friendly chemicals that can be derived from vegetable sources like glycerol and Sorbitol[10]. In all compositions a small proportions of acids like maleic, phthalic and citric acid have been added. It is biodegradable hence eco-friendly. Thus does not cause harm to environment. It is water soluble. Hence it can decay easily.

Table- 1

Composition of Sorbitol based polymers

Sr. no	**Polymer (ingredients in weight %)**	**P1**
1	Sorbitol	47.5
2	Maleic anhydride	5
3	Phthalic anhydride	5
4	Maize starch	32.5
5	Oxalic acid	5
6	Citric acid	5
7	Sodium Bisulphate	1.5
8	Sodium Bisulphite	0.5

Table-2
Physicochemical analysis of polymers

Sr. No.	Polymer	P1
1	Colour	Pale Yellow
2	Solubility	Soluble in Water
3	Consistency	Thick
4	pH	1
5	Density	1.3721
6	Surface tension	47.736
7	Viscosity	1.252
8	Acid value	11.22
10	Saponification value	137.25
11	Ester value	126.03

The physicochemical analysis of polymers is given in table-2.

The % solids indicate that all samples have 92-93.27% solids in final polymer samples. The pH of polymers (1% solution) is 3.8-4.29. The acid values of polymers show that all sample have some free acid groups. Prepared samples also have excellent viscosity of 185-200 seconds.

The composition of powder detergents based on polymer P1 is given in table-3

All samples have an alkaline pH and give excellent foaming characteristics, Surface tension and stain removing properties for stains of soil, tea, coffee. These samples are not only comparable but at times better than available commercial detergent.

The physiochemical analysis like foam, surface tension of powder detergent is given in table-4.

Compositions of powder detergents
Table -3

Name of components (in %)	PD1	PD2	PD3
Polymer	10	2.5	5
Sodium carbonate	30	35	35
Sodium lauryl ethyl sulphate	5	5	5
STPP	3	3	3
Oxalic acid (paste with sorbitol)	1	1	1
Tenopol(paste with sorbitol)	0.5	0.5	0.5
Sodium sulphate	15	18.5	15
Salt	5	5	5
Dolamite	30	30	30

Physicochemical analysis of powder detergent

Table no- 4
The physiochemical analysis like foam, surface tension of powder detergent is given in table

Sr. No.	Detergent	PD1	PD2	PD3
1	Solubility	Soluble in water	Soluble in water	Soluble in water
2	Ph	10	9	9
3	Surface tension	22.5288	24.065	23.343
4	Viscosity	0.9568	1.0014	0.9626
5	Foam value	0.6cm	1cm	1.2cm

Conclusion: Carbohydrate polymer of desired viscosity, flow, molecular weight can be prepared by using combination of sorbitol, sugar and starch. Acids such as phthalic and maleic anhydrides can be incorporated in to the composition hydrochloric acid is giving excellent results as a catalyst. The heating schedule is of 4 hrs at 120^0C.

1. The preliminary analysis indicates that polymer should be used for powder detergent compositions based on colour, viscosity, surface tension reduction and soil removing characteristics.
2. Powder detergent composition containing 10-15% of novel polymer without using conventional petroleum based actives can be used in powder detergent formulation without significant change in performance characteristics of detergent.
3. Our sample based on SLES and 10-15% novel polymer gives foaming, surface tension and detergency almost equivalent sometimes better than commercial sample.
4. The experimental compositions should be tried on pilot plant scale and market on commercial scale. This will certainly promotes “green environment”.
5. The product can be marked as free from petroleum, eco-friendly which will certainly attract global market.
6. The whitener is very important additive as it gives whiteness to the clothes.
7. Conventionally sodium chloride and dolomite are used inversely in small quantities. We have practically proved that their higher property does not affect physicochemical properties and detergency.

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9	Luca Pacioli To GAAP: How Accounting Practices Achieved Standardization	Amit Yeole, Bhushan Wankhede	61
10	A Study of Impact of COVID-19 on Education Sector in India	Ashwini Bari	68
11	A Study of Management Students' Attitude towards Online Advertising in Jalgaon District	Dr. Abhijit Salunkhe, Surekha Palve	73
12	A Study of Two Wheeler Consumer's Behavior in Bhadgaon City	Dr. B. S. Bhalerao	79
13	Evaluation of Internship Program of SNDT Women's University from Commerce Student's Perspective with Reference to the NEP 2020	Dr. Jyoti Thakur	84
14	Role of Start- Up in Entrepreneurship Development Special Reference to Marathwada Region	Dr. Lalita Yadpalwar	91
15	Shgs-Bank Linkage Programme to Protract Women Entrepreneurship	Dr. Nilesh A. Rote	100
16	Adoption of HRM Practices in Hotel Industry	Dr. Pankaj Vishwakarma, Prof. Vijay Panjabi	105
17	Work Life Equilibrium of Employees	Dr. Sahebrao Chavan	110
18	Exploring the Challenges and Prospects of NEP – 2020 in Commerce and Management Stream	Dr. Vikas M. Waghmare	113
19	A Study on Awareness of Academic Bank of Credit among Students with Reference to New Education Policy	Dr. Jyoti Thakur, Ms. Janhavi Bhosale	119
20	A Study of the Factors Affecting Employee Engagement	Ketaki Kulkarni	127
21	Navigating Change: Exploring Contemporary Trends in Commerce and Management in India	Mr. Vivek M. Morey	136
22	Myths of Indian Rural Market (An Overview)	Mr. Vinod S. Khair, Dr. Yogesh V. Toravane	141

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Navigating Change: Exploring Contemporary Trends in Commerce and Management in India

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Abstract:

This research paper investigates the contemporary trends in commerce and management within the dynamic landscape of India. Through a comprehensive literature review and empirical analysis, we identify and analyze the latest trends shaping these domains. Our research utilizes a mixed-methods approach, combining qualitative and quantitative data collection methods to gain a holistic understanding of these trends. Key findings include the emergence of e-commerce, digital marketing strategies, sustainable business practices, and agile management approaches as significant trends. We also explore the impact of these trends on Indian businesses and offer recommendations for organizations and policymakers. Understanding and adapting to these trends are critical for businesses seeking to thrive in the evolving Indian market.

Keywords: Commerce trends, Management trends, India, E-commerce, Digital marketing, Sustainable business practices, Agile management, Business impact, Recommendations, Emerging markets.

Introduction:

The world of commerce and management is in a state of constant evolution, and perhaps nowhere is this more evident than in the bustling and diverse market of India. In recent years, India has witnessed transformative changes in its business landscape, driven by technological advancements, shifting consumer preferences, and global economic dynamics. As such, this research paper seeks to shed light on the new trends that are shaping commerce and management practices within this vibrant subcontinent. Understanding and adapting to the evolving landscape of commerce and management in India is of paramount importance for various stakeholders. For businesses, staying ahead of the curve is imperative for sustainable growth and competitiveness. Policymakers need to be informed about these trends to formulate strategies that foster economic development and regulatory frameworks. Educators must prepare future professionals with the skills and knowledge necessary to excel in this rapidly changing environment.

Objectives:

1. To identify and analyze the most influential and emerging trends in commerce and management in India.
2. To explore the impact of these trends on businesses, industries, and the economy.
3. To provide insights and recommendations for businesses, policymakers, and educators on how to navigate and leverage these trends effectively.

Discussion

1. E-commerce and Digitalization:

Existing literature consistently emphasizes the rapid growth of e-commerce in India. Studies highlight the rise of major players like Flipkart and Amazon and their impact on

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traditional retail. However, there is a need for more nuanced analyses, including the role of smaller e-commerce ventures and the implications for supply chain management.

2. Digital Marketing Strategies:

Scholarly work often discusses the increasing importance of digital marketing in reaching Indian consumers. The literature covers topics such as social media marketing, influencer marketing, and SEO optimization. However, there's room to explore the effectiveness of these strategies across various industry sectors.

3. Sustainable Business Practices:

Sustainability is gaining prominence in Indian business discussions. Research often touches on corporate social responsibility (CSR) initiatives, but there's an opportunity to delve deeper into the integration of sustainability into core business strategies and its long-term impact on competitiveness.

4. Agile Management Approaches:

Agile management practices, borrowed from the tech industry, are becoming popular among Indian businesses. The literature recognizes this trend but lacks in-depth analyses of its adoption, challenges faced by traditional organizations, and the cultural factors influencing its implementation.

5. Impact of Regulatory Changes:

India has witnessed significant regulatory changes, such as the introduction of the Goods and Services Tax (GST) and reforms aimed at ease of doing business. Existing research discusses these changes but may not provide a holistic view of their effects on commerce and management practices.

6. SMEs and Startups:

While there's a growing interest in the startup ecosystem in India, there's still limited research on the unique management challenges faced by small and medium-sized enterprises (SMEs) and startups, especially in tier 2 and tier 3 cities.

7. Talent Management and Skill Development:

As the Indian workforce evolves, there's a need for research on talent management practices, the role of upskilling and reskilling, and the impact of these factors on organizational performance.

Emerging Trends in Commerce in the Indian Context:

The commerce landscape in India has witnessed dynamic changes in recent years, driven by technological advancements, changing consumer behavior, and regulatory developments. Here are some of the most prominent and recent trends:

1. **E-commerce Dominance:** E-commerce has experienced explosive growth, with major players like Flipkart, Amazon, and Reliance Retail's JioMart leading the way.
2. **Online Grocery Shopping:** The convenience of online grocery shopping has gained immense popularity, particularly during the COVID-19 pandemic.
3. **Digital Payments:** The adoption of digital payment methods, including mobile wallets and UPI (Unified Payments Interface), has surged.
4. **D2C (Direct-to-Consumer) Brands:** Direct-to-consumer brands have disrupted traditional distribution channels, offering unique products directly to consumers.

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5. **Sustainability Initiatives:** Environmental and social responsibility has become focal points, with consumers seeking eco-friendly and ethical brands.
6. **Hyperlocal Delivery Services:** Hyperlocal delivery startups have emerged, connecting local retailers with nearby customers.
7. **Omni channel Retailing:** Traditional retailers are embracing omnichannel strategies, integrating online and offline shopping experiences.
8. **Personalization and AI:** AI-powered personalization is enhancing the shopping experience, with recommendation engines and chat bots.

Emerging Trends in Management in the Indian Business Landscape:

The management practices in the Indian business landscape have been evolving to adapt to the changing global and domestic dynamics. Here are some contemporary management trends:

1. **Agile Management:** Agile management methodologies, initially popularized in the IT sector, are now spreading to various industries in India.
2. **Remote Work and Hybrid Models:** The COVID-19 pandemic accelerated the adoption of remote work and hybrid work models.
3. **Diversity, Equity, and Inclusion (DEI):** Companies are focusing on fostering diverse and inclusive workplaces.
4. **Digital Transformation:** Embracing digital technologies to streamline operations and enhance customer experiences.
5. **Sustainability and CSR:** Integrating sustainability into business strategies and corporate social responsibility (CSR) initiatives.
6. **Employee Well-being:** Prioritizing the mental and physical well-being of employees.
7. **AI and Analytics:** Leveraging artificial intelligence and data analytics to make data-driven decisions.

Impact and Implications of Emerging Trends on Businesses, Industries, and the Indian Economy:

1. Impact on Businesses:

Positive Impact: Many businesses have benefited from e-commerce and digitalization trends by reaching a broader customer base and improving operational efficiency.

Negative Impact: Traditional retailers may face increased competition and need to adapt to omnichannel strategies.

2. Impact on Industries: Positive Impact: Industries related to technology, e-commerce, and digital marketing experience significant growth and job creation.

Negative Impact: Traditional industries may face disruption and need to transform to remain competitive.

3. Impact on the Economy:

Positive Impact: E-commerce and digital payment trends contribute to economic growth, while sustainability initiatives can reduce environmental impact.

Negative Impact: The digital divide can exacerbate income inequality if not addressed.

4. Implications for Business Strategies:

Adaptation: Businesses need to adapt to digitalization, e-commerce, and agile management practices to remain competitive.

Sustainability Integration: Integrating sustainability into business strategies can enhance brand reputation and customer loyalty.

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5. Implications for Management Practices:

Agile Management: Organizations should adopt agile management practices to respond quickly to market changes and enhance project delivery.

Remote Work: Continued support for remote work and hybrid models can improve employee satisfaction and attract top talent.

6. Implications for Startups and SMEs:

Opportunity: Emerging trends provide opportunities for startups and SMEs to innovate and gain market share.

Challenges: These businesses may face resource constraints and competition from established players.

Challenges and Obstacles Associated with Adopting Emerging Trends:

1. Digital Divide: The digitalization trend may exclude segments of the population with limited access to technology. This poses challenges for businesses trying to reach diverse customer groups.

2. Regulatory Complexity: Rapid e-commerce growth has led to regulatory complexities, including taxation and data privacy issues. Navigating these regulations can be challenging for businesses.

3. Supply Chain Disruptions: While e-commerce offers growth opportunities, it also exposes businesses to supply chain disruptions, affecting inventory management and timely deliveries.

4. Talent Shortage: The adoption of digital technologies and agile management requires a skilled workforce. Finding and retaining such talent can be a challenge.

5. Sustainability Implementation: Integrating sustainability practices can be resource-intensive and complex for businesses, especially in industries with high environmental impacts.

Future Directions in Commerce and Management in India:

1. Tech-Driven Innovation: Technology will continue to be at the forefront of commerce and management. Businesses will innovate with AI, IoT, and blockchain to enhance efficiency and customer experiences.

2. Sustainable Business: Sustainability will become a central theme, with more companies adopting circular economy practices and reducing their carbon footprints.

3. E-commerce Evolution: E-commerce will diversify beyond traditional retail, with sectors like healthcare, education, and agriculture embracing online platforms.

4. Personalized Customer Experiences: Businesses will increasingly use data analytics and AI to provide highly personalized and relevant customer experiences.

5. Resilient Supply Chains: Companies will invest in resilient and flexible supply chains to withstand disruptions.

6. Workplace Flexibility: Remote and hybrid work models will become permanent features, with businesses focusing on employee well-being and engagement.

7. Social Impact Initiatives: More businesses will engage in DEI and social impact initiatives to align with changing consumer values.

8. Government Initiatives: Government policies will play a crucial role in shaping the future, with an emphasis on digital infrastructure, sustainability incentives, and regulatory clarity.

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Conclusion:

1. E-commerce Dominance: E-commerce has emerged as a driving force in the Indian market, reshaping how businesses connect with consumers.

2. Digital Transformation: The adoption of digital technologies, including digital payments and marketing strategies, has revolutionized the way businesses operate.

3. Sustainability Imperative: Sustainability practices are no longer optional; they have become a crucial aspect of business strategies, aligning with changing consumer values.

4. Agile Management: Agile management methodologies have gained prominence, enabling businesses to respond swiftly to market changes and enhance project delivery.

5. Diversity and Inclusion: Diversity, equity, and inclusion initiatives are fostering inclusive workplaces and resonating with consumers.

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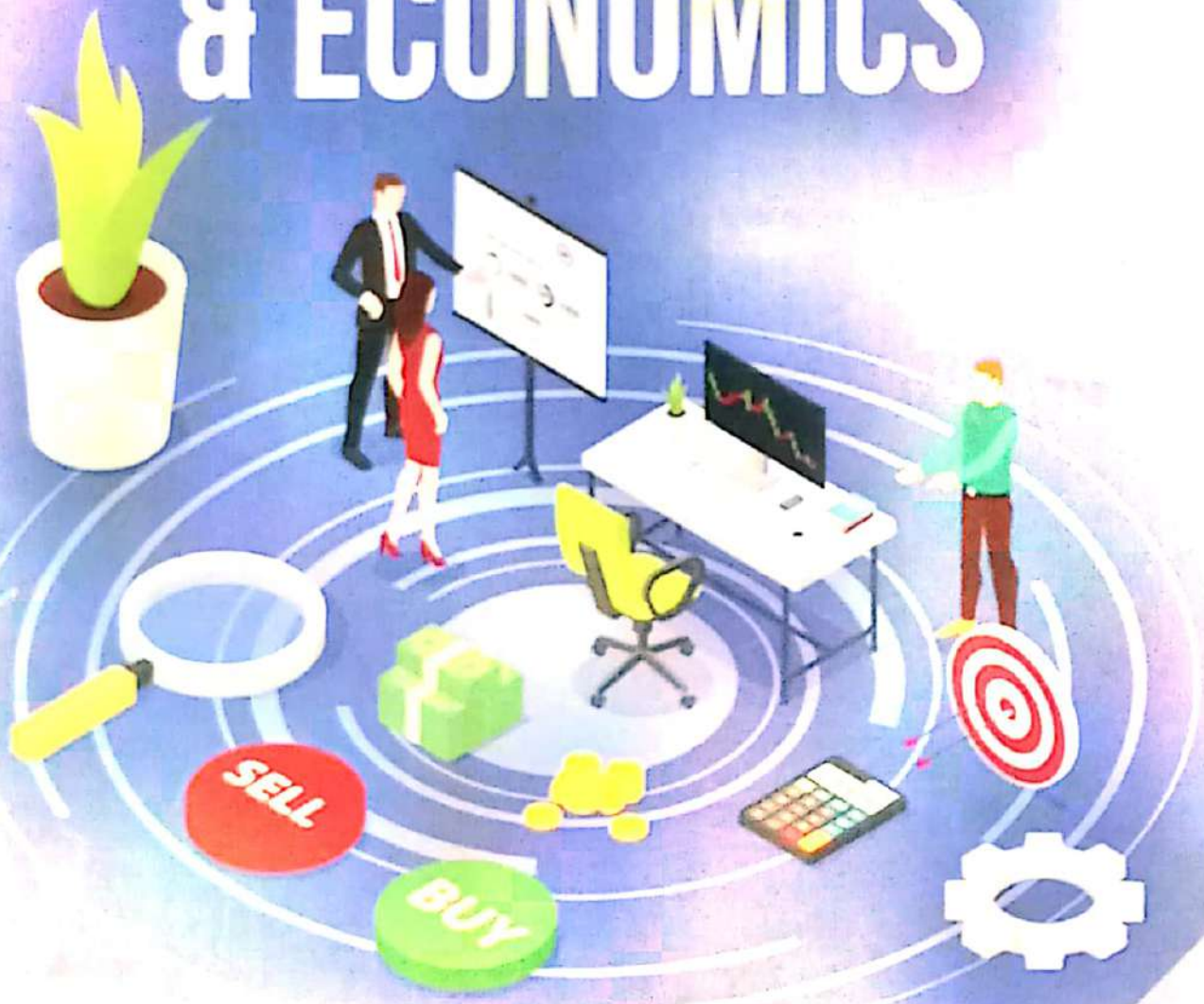
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Academic year
2023-24

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INDEX

Sr No.	Article/ Author	Page No.
०१.	**आपूर्ति श्रृंखला प्रबंधन** डॉ.सुरेश एन.गवई	०५
०२.	**क्रिप्टोकरन्सी – कार्य, प्रकार, फायदे, तोटे** प्रा. डॉ. जया सवाईथूल	१४
०३.	**भारतातील विविध पीक विमा योजनांचा आढावा** संगिता महादेव शेगोकार	२३
०४.	**ग्रीन मार्केटिंग – एक नवीन विपणन प्रणाली** **Dr. Savita V. Nichit**	३०
०५.	**जागतिकीकरण एक काळाची गरज** प्रा. डॉ. एन. एन. धोंडगे	३६
०६.	**PMFBY योजनेचा लाभ शेतकऱ्यांना कि विमा कंपन्यांना : एक अभ्यास** रोशनी सु. तट्टे । प्रा डॉ प्रशांत वैराळकर	४०
०७.	**जागतिकीकरणाचा भारतीय अर्थव्यवस्थेवर पडलेला परिणाम** प्रा. डॉ. अमोल सतीश राऊत	४६
०८.	**ई–कॉमर्स आणि डिजिटल मार्केटिंगची व्युहरचना** कु. अपेक्षा घ. दुबें । प्रा डॉ प्रशांत वैराळकर	५१
०९.	**ई–कृषी विपणन विकास.** प्रा.डॉ. सतीश राणे.	५
१०.	**वित्तीय पद्धती (Payment system) व अंकिय पॉकेट (Digital Wallet) मधील आधुनिक संकल्पना व विस्तार** कु.विशाखा व्ही. पाटील । प्रा डॉ प्रशांत वैराळकर	५
११	**बँकिंग सेवा** प्रा. डॉ. प्रविण कुलकर्णी	६
१२	**भारतीय अर्थव्यवस्थेवर कोविड– १९ चा परिणाम व पुनर्प्राप्ती धोरण** **Mr. Dipak J. Chavan**	७

Scanned with OKEN Scanner

24.	**Research Methodology in Business and Management** Mr. Bhushan Shrirampant Mangate	18
25.	**The Effects of Recent Trends on E-Commerce Business, in 21st Century** Dr Wasudeo Dattatray Golait	19
26.	**Sustainable Development and Management: A Holistic Approach for a Better Future** Dr. Ambadas B. Pande	20
27.	**E-commerce Impact On Business** Prof. Ganesh S. Kiroche	21
28.	**Indian Agriculture: Performance And Challenges** Dr.Madhuri Kishanrao Tanurkar	22
29.	**Opportunity for Sustainable Development of Villages through Cottage Industries.** Dr. Sanjay M. Kherde/ Dr. Manish D. Jadhav	23
30.	**Role Of Accounting Study In Indian Economy.** Dr. Ganesh M. Khekale	24
31.	**A Critical Study of Digital Payment System in India** Dr. S. K. Rodde	24
32.	**A Case Study on Strawberry Production and Marketing in Chikhaldara** Prof. Ashish Rameshlal Kanhu	25
33.	**E-Commerce and Digital Marketing Strategies: Harnessing the Power of the Digital Landscape for Business Success** Mr. Vivek Mohan Morey	26
34.	**Impact of Blockchain Technology In E-Commerce** Dr. Santosh Bansirao Gaikwad	27

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33 E-Commerce and Digital Marketing Strategies: Harnessing the Power of the DigitalLandscape for Business Success

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Abstract:

This research paper delves into the realm of e-commerce and digital marketing strategies and their profound impact on contemporary businesses. The primary objectives of this study are to analyze the current e-commerce landscape, explore various digital marketing tactics, and investigate how their integration can bolster online presence and drive business success. To achieve these goals, a comprehensive literature review was conducted, examining pertinent theories and successful case studies. The chosen methodology included data collection through surveys and interviews, followed by qualitative data analysis. The key findings highlight the significance of adopting digital marketing strategies in the rapidly evolving e-commerce landscape. Successful integration of e-commerce platforms with effective digital marketing campaigns enhances customer engagement, increases conversion rates, and fosters sustainable growth. Ethical considerations and legal frameworks surrounding data privacy and online advertising are crucial for businesses to navigate. The paper concludes with future trend predictions, enabling businesses to stay competitive and adaptive in the dynamic digital sphere.

Introduction:

In today's fast-paced and interconnected world, e-commerce and digital marketing have emerged as pivotal components of the business landscape, revolutionizing how companies interact with consumers and conduct their operations. E-commerce refers to the buying and selling of goods and services through electronic channels, predominantly the internet. Digital marketing, on the other hand,

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encompasses various online tactics used to promote products, engage customers, and build brand awareness. Together, these two domains have reshaped the way businesses function, making them indispensable in gaining a competitive edge and sustaining growth. The significance of this research lies in comprehending the symbiotic relationship between e-commerce and digital marketing and how their seamless integration can fuel business success. As traditional marketing methods gradually make way for digital strategies, it is essential to understand the evolving landscape to leverage its potential fully.

Objectives:

) The first objective is to delve into the current state of e-commerce, exploring market trends, consumer behavior, and the impact of technological advancements. By understanding the present dynamics, businesses can devise tailored strategies to meet customer expectations and stay ahead in the competitive market.

) To delve into the vast array of digital marketing tactics employed by businesses. These may include social media marketing, content creation, search engine optimization (SEO), email marketing, and influencer campaigns. Examining successful case studies of companies that have effectively utilized these strategies will offer valuable insights into their potential impact.

Literature Review:

Consumer Behavior in E-commerce:

Studies have explored consumer behavior in the context of online shopping. The Theory of Planned Behavior and Technology Acceptance Model have been commonly used to understand consumers' intentions and attitudes towards e-commerce platforms. Understanding factors that influence purchase decisions, such as trust, perceived usefulness, and perceived ease of use, helps businesses design user-friendly websites and targeted marketing campaigns.

Digital Marketing Strategies:

The literature reveals a plethora of digital marketing tactics and their efficacy in reaching and engaging target audiences. Content marketing, social media marketing, and influencer marketing have emerged as powerful tools in building brand

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awareness and driving customer engagement. Research emphasizes the importance of creating valuable content and establishing authentic connections with customers to foster brand loyalty.

3. Personalization and Customer Experience:

Personalization has been identified as a key driver of customer satisfaction and retention in e-commerce. Tailoring product recommendations, content, and offers based on individual preferences and behaviors enhances the overall customer experience. Studies show that companies that implement effective personalization strategies witness improved conversion rates and higher customer lifetime value.

4. Mobile Commerce (m-commerce):

With the increasing use of smartphones, m-commerce has gained significant attention in the literature. Mobile optimization of websites and apps, coupled with targeted mobile marketing campaigns, have become crucial for businesses to tap into the growing base of mobile consumers. Understanding mobile user behavior and preferences is vital for successful m-commerce implementation.

Methodology:

This Research Paper prepare based on secondary data has collected from research paper, newspaper, article, website and report of State & Central government and nongovernment agencies.

E-commerce Landscape Analysis:

The current e-commerce landscape is a dynamic and rapidly evolving arena shaped by technological advancements, changing consumer behaviors, and market trends. Understanding this landscape is crucial for businesses aiming to capitalize on emerging opportunities and stay competitive. Here's an overview of key aspects within the e-commerce landscape:

1. Market Trends:

a. Rapid Growth: E-commerce has witnessed exponential growth, with an increasing number of consumers opting for online shopping due to convenience, wider product choices, and competitive pricing.

b. Global Reach: The digital nature of e-commerce enables businesses to transcend geographical boundaries and tap into international

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markets, expanding their customer base.

Mobile Commerce (m-commerce): The proliferation of smartphones has led to a surge in mobile shopping. Businesses are prioritizing mobile optimization to cater to the growing number of mobile shoppers.

Consumer Behavior:

Omni-channel Shopping: Consumers expect a seamless shopping experience across various channels, blending online and offline interactions.

Personalization: Consumers respond positively to personalized shopping experiences, from tailored product recommendations to customized marketing messages.

Social Commerce: Social media platforms are becoming avenues for shopping, with "buy" buttons and integrated shopping features, blurring the lines between social interaction and online purchasing.

Emerging Technologies:

Artificial Intelligence (AI): AI is revolutionizing e-commerce through chatbots, virtual shopping assistants, and personalized recommendations based on user behavior.

Augmented Reality (AR) and Virtual Reality (VR): AR and VR technologies allow consumers to visualize products before purchase, enhancing the online shopping experience.

Voice Commerce: Voice-activated devices like smart speakers are changing how consumers search for products and make purchases, driving the need for voice-friendly shopping interfaces.

Blockchain and Cryptocurrencies: These technologies are being explored for secure and transparent transactions, potentially transforming payment systems in e-commerce.

Sustainability and Ethical Consumption:

Environmentally Conscious Choices: Consumers are showing a growing preference for brands that prioritize sustainability, leading to the rise of eco-friendly products and packaging.

Ethical Practices: Businesses that transparently communicate ethical sourcing, fair labor practices, and social responsibility initiatives are gaining consumer trust.

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5. Data Privacy and Security:

a. Heightened Concerns: High-profile data breaches have raised consumer concerns about data privacy. Businesses must prioritize robust data security measures to maintain trust.

Digital Marketing Strategies in E-commerce:

Digital marketing strategies are integral to the success of e-commerce businesses, as they enable companies to connect with their target audience, drive traffic, and enhance conversions. Here's an exploration of some key digital marketing strategies commonly used in e-commerce:

1. Social Media Marketing:

Social media platforms (such as Facebook, Instagram, and Twitter) are utilized to build brand awareness, engage with customers, and showcase products through visually appealing content.Businesses often leverage influencer partnerships and user-generated content to reach wider audiences.

2. Content Marketing:

Content marketing involves creating valuable, informative, and relevant content to attract and retain customers. Blog posts, videos, infographics, and how-to guides establish brands as authoritative sources in their industry.

3. Search Engine Optimization (SEO):

SEO techniques optimize websites to rank higher in search engine results pages (SERPs). By optimizing keywords, meta descriptions, and building quality backlinks, businesses can improve their online visibility and organic traffic.

4. Email Marketing:

Email marketing involves sending targeted emails to customers to nurture relationships, promote products, and drive sales. Segmentation and personalization are key to delivering relevant content to subscribers.

Integration of E-commerce and Digital Marketing:

The integration of e-commerce platforms with digital marketing strategies is essential for businesses aiming to create a cohesive online presence, engage customers effectively, and drive sales. Here's how businesses can successfully merge these two realms:

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Unified Brand Experience:

nsure consistency: Maintain consistent branding across e-mmerce platforms and digital marketing channels. The look, feel, d messaging should align to create a seamless brand experience.

Data-Driven Insights:

alytics integration: Use data from e-commerce platforms and ital marketing campaigns to gain insights into customer behavior. alyze trends, identify high-performing products, and understand at marketing efforts resonate with your audience.

Personalization and Segmentation:

geted campaigns: Utilize e-commerce data to segment customers ed on past purchases, preferences, and browsing history. Create eted digital marketing campaigns that resonate with specific tomer segments.

Omni-channel Approach:

lti-channel engagement: Leverage various digital marketing nnels (social media, email, search) to guide customers through the mmerce journey. Ensure consistent messaging and offers across forms.

ocial Commerce:

pping features: Utilize social media platforms with shopping ures to enable customers to purchase directly from posts. Utilize pable tags and links to enhance the shopping experience.

ontent Integration:

duct-related content: Seamlessly integrate product information, ews, and user-generated content from your e-commerce platform your digital marketing efforts. This provides social proof and nces credibility.

etargeting and Remarketing:

ndoned cart campaigns: Use digital marketing channels like il and display ads to retarget users who abandoned their carts, nding them of their incomplete purchase and offering incentives to plete the transaction.

llenges in Adopting E-commerce and Digital Marketing tegies:

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1. Digital Transformation Resistance:

Challenge: Traditional businesses may face resistance from employees and management in adopting new e-commerce and digital marketing practices due to a lack of familiarity or fear of change.

Solution: Implement change management strategies, provide training, and communicate the benefits of digital transformation.

2. Data Privacy Concerns:

Challenge: Collecting and handling customer data for e-commerce and digital marketing can raise privacy concerns. Stricter regulations (like GDPR) require businesses to be transparent and responsible in data usage.

Solution: Implement robust data protection measures, obtain user consent, and comply with relevant regulations to build and maintain customer trust.

3. Technological Barriers:

Challenge: Smaller businesses might struggle with the cost and complexity of setting up and maintaining e-commerce platforms and digital marketing tools.

Solution: Opt for user-friendly e-commerce platforms, leverage cloud-based solutions, and consider outsourcing certain aspects to experts.

4. Intense Competition:

Challenge: The digital landscape is crowded, and businesses face stiff competition. Standing out and attracting customers require innovative strategies.

Solution: Focus on unique value propositions, create compelling content, and leverage data-driven insights to tailor marketing efforts.

Opportunities for Growth and Innovation in the Digital Space:

1. Personalization and Customer Experience:

Opportunity: Businesses can leverage data to create highly personalized experiences, from tailored product recommendations to personalized marketing messages.

2. Artificial Intelligence (AI) Integration:

Opportunity: AI-powered chatbots, recommendation engines, and predictive analytics can automate processes and provide

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customers with real-time assistance.

3. Voice Commerce:

Opportunity: The rise of voice-activated devices presents a new channel for e-commerce. Optimizing for voice search and enabling voice-based transactions can tap into this growing trend.

4. Virtual and Augmented Reality:

Opportunity: AR and VR technologies can enhance the online shopping experience by allowing customers to virtually try products before purchase. Increased customer engagement, reduced return rates, and differentiation from competitors.

Conclusion:

In conclusion, this research paper delved into the dynamic realm of e-commerce and digital marketing strategies, uncovering key insights that underscore their crucial role in modern business success. The research examined the current e-commerce landscape, revealing its rapid growth, changing consumer behaviors, and the emergence of transformative technologies. Through a comprehensive review of literature, a mixed-methods approach was employed to explore the integration of e-commerce platforms with various digital marketing strategies. The study unveiled the significance of seamless integration between e-commerce and digital marketing, demonstrating how a unified brand experience, data-driven insights, and personalized approaches can drive customer engagement and boost sales. By adopting an omni-channel approach, leveraging social commerce, and optimizing content, businesses can effectively enhance their online presence and capitalize on the evolving digital landscape. In a competitive environment marked by challenges such as digital transformation resistance, data privacy concerns, and technological barriers, businesses that navigate these hurdles can tap into abundant opportunities for growth and innovation. By embracing personalization, AI integration, emerging technologies, and sustainable practices, companies can differentiate themselves, expand their customer base, and thrive in the digital space.

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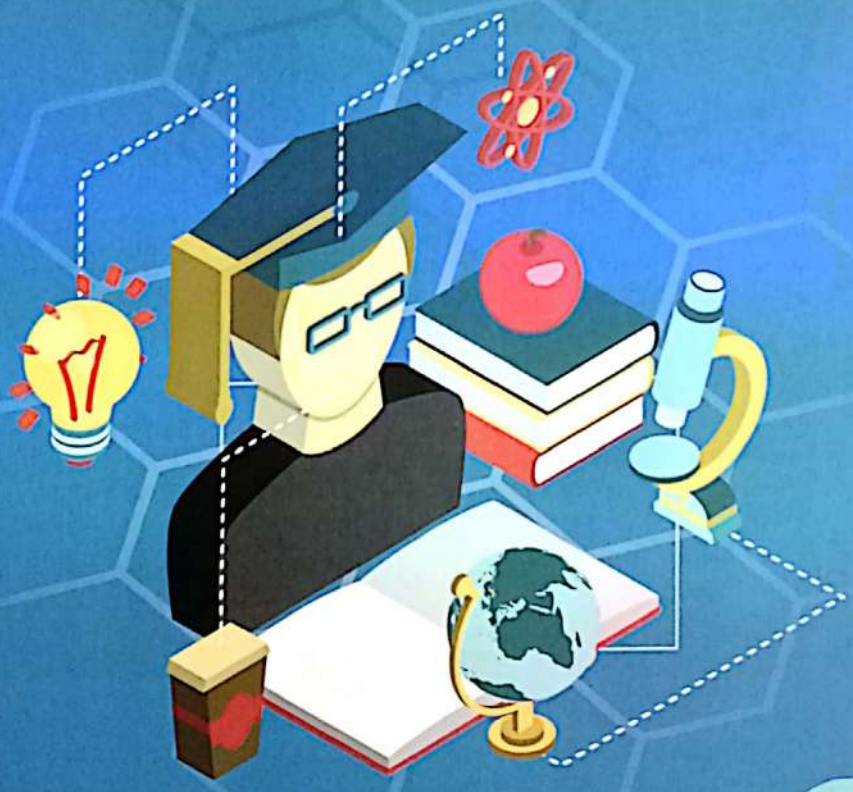
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36.	**Employability of Business Education in India** Dr. Vivek M. Morey	175-179
37.	**What is National Education Policy 2020: What's the benefit of NEP to stake holders (Parent, Student, Teacher) as a Higher Education Institute?** Prof. Ashish Rameshlal Kanhu	180-185
38.	**Job Satisfaction and Impact of NEP on The Creation of New Job** Shri. Bharat S. Deshmukh	186-189
39.	**NEP 2020 and Online Education - Benefits and Challenges** Dr. Ashish P. Mohata	190-195
40.	**An Efficient Architecture For Mobile Web Services in Cloud Environment** Dr. Dudhe Anil A., Dr. Sherekar S.S.	196-201
41.	**Impact of New Education Policy 2020 on Higher Education** Dr. Rupesh S. Mankar	202-207
42.	**Comparison of National Education Policy 1986 And New Education Policy** Dr. Sanjivani K. Parate	208-211
43.	**NEP 2020: Features of NEP 2020 and Role of Teacher in NEP 2020** Dr. Santosh P. Rathod	212-216
44.	**भारतातील आरक्षण आणि राजकारण** प्रा. डॉ. अरुण मुकुंदराव शेळके	217-219
45.	**भारत की नई शिक्षा नीति – विशेषताएँ, गुण एवं दोष** डॉ. जे. एस. सवाईथूल	220-224
46.	**राष्ट्रीय शिक्षा नीति के माध्यम से भारतीय भाषाओं कला और संस्कृति का संवर्धन** डॉ. आनंद आर. वक्षी	225-227

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Employability of Business Education in India

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Abstract

The purpose of this research is to study the development and employability of busine education in India. The secondary data is used for the study. The study find out that manageme institutes giving management education in the country have grown with rapid speed. The no. management institutes and no. of students enrolled for business education also increased. But t rate of employability in business education was less than 50% up to the year 2019. There is slig change from the year 2020 and in the year the employability rate shows a rising percentage of 55 Lack of skills was the reason for low employability. To increase the employability the focus should on providing knowledge and developing skills i.e. English language skill, communication ski managerial skills, grooming skills and analytical skills etc.

Key Words- commerce, commerce educations, business education, employability, skills.

Introduction

The world is entering a new age of global competition, modern technology, intellectu properties and the age of complexity. Every country is running full speed of progress, going flat o just to stay in the same place. Even small business now aspires to recruit 'right man for the right jo since the demands of the business have undergone a drastic change. Businesses expect smart worki employees who can appreciate the contemporary issue of today than hardworking employees wi high academic standards. They expect new recruits to understand the environment well and be in position to deliver results in a globalized world. After 1991, business in India has witness unprecedented change partly under the pressure of globalization and policy shifts from regulation deregulation, from state control to private initiative and from domestic focus to global focu Leadership, teamwork, entrepreneurship, risk taking, conflict management, attitude and motivatio service orientation and change in mind are emerging as centerpieces of curriculum for imparti effective commerce education in the fast changing world. To find out whether the prese Management education caters the job requirements of modern industries, the researcher has select the subject 'Employability of Business education in India'.

Review Of Studies :

1. Sangeeta Sahney et al (2004) pointed Indian educational system has been subjected to fa radical, and ever revolutionary change over recent years.
2. Sahu K.C(1991) emphasized that values are of utmost importance and are inseparal irrespective to any form of education Management education should produce persons with su value orientation, who, through example of dedicated hard work in a spirit of service, c change the attitude of the people they manage towards work, and towards each other to ensu

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quality of life and of work life.

Basu Sharma et al (1996) pointed out that internationalization of management has been promoted along several dimensions such as curricula challenge, research activities with both contents and outlet being relevant and executive development programs. It seems that educational institutions and supplementary providers of management education have no choice but to rise to the challenge of global competition.

ctives of The Study

To study the concept of commerce, commerce education and business education

To study the development of business education in India

To study the employability of business education in Indian context

To find out the reasons of low employability of business education in India.

To make recommendations for improvement in employability.

arch Methodology

All the information and data presented in this paper were gathered from various sources of ndary data. The sources came from online search database from Multimedia University Library site's online databases. The online search database provided secondary data like journals and cts from newspapers, books and magazines. Some of the information and data were obtained the Internet search engines like Google, Yahoo.

ning Of Commerce , Commerce Education And Business Education Commerce:

Commerce in nothing but it is an organized system for the exchange of goods between the bers of the industrial world. According to James Stephenson "Commerce is that part of business h is concerned with the exchange of goods and services and includes all those activities which tly or indirectly facilitate that exchange."

mmerce Education:

Commerce education is a type of training which, while playing its part in the achievement of general aims of education of any given level, has for its primary objective the preparation of le to enter upon a business career, or having entered upon such a career, to render more efficient ice therein and to advance from their present level of employment to higher levels.

Leverett. S. Lyen defined commerce education as "any education which a business man has which makes him a better businessman, is for him business education, no matter whether it was ined in the walls of a school or not".

ning of Business Education:

According to some writers commerce education is a part of business education. A agement teacher Dey (1996) has mentioned as "however, it should be clear that the management cation and Commerce Education are nothing but the two branches of business education.

Some writers opinioned that there is difference between the commerce education and ness education so far as the approach of the course curriculum is concerned. "Parida and Parida 96) have pointed that the approach of commerce education and business education is different n each other. They have clearly stated as "the priory, for the Indian economy is to go for ellency in business education. We have IIMs and private management institutes for imparting

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same."

Development of Business Education in India

The Commerce education that was being imparted in the colleges and universities was not sufficient to meet the requirement of the business houses. So in India branches like management education and other professional courses emerged despite having a full-fledged commerce education being imparted by universities. Indian Institute of Social science start India's first management programme in 1948 and stated as "intended to systematically train manpower, create and spread the knowledge required for managing industrial enterprises in India. The Xavier Labour Relations Institute set up at Jamshedpur in the city of TISCO. The University of Calcutta initiated in setting up of the Indian Institute of Social Welfare and Business Management, India's first official management institute. Government of India applies to the Ford Foundation in 1961 to launch two Indian Institutes of Management at Kolkata and Ahmadabad. Thus came into existence Indian Institute of Management Ahmedabad (IIMA), followed soon after by one in Kolkata (IIMC). Starting with the establishment of 4 Indian Institutes of Management Calcutta (1961), Ahmedabad (1962), Bangalore (1973), Lucknow (1984), now management education is being offered as full time/part time MBA programmes by some leading universities in the country. Recently and particularly during the last 4-5 years the country has witnessed a tremendous growth in the founding of management institutions most of them in private sector offering management programs in different functional areas of management.

Employability of Business Education in India

Management institutes in the country have grown with rapid speed from just 200 managements institutes in nineties to more nearly 3500 college presently. The number of MBA seats in the country has gone up from just under 95,000 in 2007 to 350,000 in the year 2012. The quantity of seats increased at an annual growth rate of 30 per cent. The quality of education apparently did not keep pace. It suffers from the same malaise as much of India's higher education sector. While supply has risen to meet the fast-growing demand, lack of quality control has meant India has thousands of youngsters armed with a degree but with nowhere to go. Where management education in India actually differs from the broader higher education space is in the topnotch quality of the best institutions. IIM, Ahmedabad, which tops the Business Today rankings in 2012, features in the Top 10 of the very prestigious Financial Times (FT) rankings of the world's best business schools. IIM Ahmadabad is ranked second in the Asia-Pacific region by the QS 200 rankings of global business schools in 2012. The QS rankings feature six Indian B-schools in the top 36 from Asia-Pacific, which are also in the top 200 in the world. The Indian School of Business, Hyderabad, ranks 20 in the FT rankings for 2012.

A survey of India's top 100 business schools revealed a majority of MBA graduates in India are not employable. The survey, which covered 2,264 MBA students from 29 cities, showed that outside the top 25 business schools, the remaining provided only 21 per cent of their graduates with a job. The employability of MBA graduates from schools ranked between 26 and 100 was actually worse in 2012 (21 per cent) than in 2007 (25 per cent), when the previous survey was conducted. According to recent survey findings the employability of management students remains below 10% for any functional role in fields such as HR, Marketing or Finance.

As per the National Employability Report prepared by Aspiring Minds, employability of management graduates is at the lowest level especially in the field of business consulting followed by analyst and functional roles. Aspiring Minds COO and CTO Varun Aggarwal said, "there is an urgent need to audit whether we are training industry-ready individuals." During the survey the company asked questions to 32,000 students from more than 220 MBA schools. However the B-Schools pa

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special attention towards building capacity in management education but the same can't be practiced for building employability of the candidates.

Reasons of Low Employability

A survey conducted by IIM alumni and faculty brought to light the major reasons for which so many of the students remain unemployed. The reason for this is that the industry is looking for not just a degree from a good institute but some basic skills which most of the students were lacking. A survey revealed that there are 9 missing skills which a company looks for in a student. These skills are

1. Business communication,
2. Grooming skills,
3. Right attitude,
4. Practical domain knowledge,
5. Basic corporate awareness,
6. Some work experience,
7. Analytical ability,
8. Knowledge about sales and marketing and
9. Basic managerial skills.

One more reason for low employability is that for students in tier II and tier III cities, a large gap is observed in English language skills and Finance. Even if candidates from non-metro cities pursue their education in MBA schools in metros, their disadvantage in English and Finance is not completely eradicated. The gap in other modules pretty much closes. It is also observed that Finance is the hardest-to-attain skill for non-specialists (those in HR and Marketing domain). Also, the importance of English in the job market cannot be overemphasized. On the other hand, given the importance of finance education for job in the BFSI industry and the general need of financial literacy for better management of personal money, lack of finance education is certainly a big concern.

National Education Policy-2020-

Following the release of the Draft New Education Policy-2019 by the Ministry of Human Resource Development, a series of public consultations were held. It is a significant and critical reform in the country's whole education system after a 34-year hiatus. It discusses curriculum content reduction in order to improve essential learning, critical thinking, and more holistic experiential, discussion-based, and analysis-based learning. It also discusses a curriculum and pedagogical structure revision from a 10+2 system to a 5+3+3+4 system design in an effort to optimise learning for students based on the cognitive development of children. On July 29, 2020, the cabinet approved the New National Education Policy with the goal of introducing several changes to the existing Indian education system. It will be available in India until 2026.

National Education Policy-2020 and Vocational Education

The New Education Policy has a target to achieve at least 50% of learners through the school and higher education system shall have exposure to vocational education. It is the first time in history that any education policy has a crystal-clear objective for vocational education. To attain this objective a clear action plan with targets and timelines are to be developed. The policy intended to remove the social status hierarchy associated with vocational education and integration vocational education into mainstream education in all educational institutions in various phases. It will start with vocational exposure at an early age in middle and secondary school. Considering the need for vocational education, It has also been decided that high-quality vocational education will be seamlessly integrated into secondary and higher education. The policy's goal is for every child to learn at least one vocation and be exposed to several others. This would result in a greater emphasis on the dignity of labour and the significance of various vocations involving Indian arts and craftsmanship. By 2025, at least half of all learners in the school and higher education systems will have

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had exposure to vocational education.

Conclusion

Management institutes in the country have grown with rapid speed. The no of institutes giving business education increased in India. The no. of students enrolled for business education also increased. But the rate of employability in business education up to the year 2019 was less than 50%. There is slight change from the year 2020 and in the year the employability rate shows a rising percentage of 55%. To increase the employability the focus should be on providing knowledge and developing skills i.e. communication skill, managerial skills, grooming skills and analytical skills.

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Index

Sr. No.	Contents	Page No.
1.	"रोग ही विश्वव्यापी सामाजिक घटना आहे एक समाजशास्त्रीय अध्ययन " – डॉ. आनंदा भिकुजी काळे	१–८
२.	**अरुणा ढेरे यांची कविता : एक अभ्यास** – डॉ.निता उ.मेश्राम	9–16
3.	**ठुमरी की विभिन्न शैलियाँ** **– अलिश मोहन**	**17–29**
4.	**दोन प्रकारचे शोध असतात** – प्रा. डॉ. मुकेश सरदार	30–33

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4. दोन प्रकारचे शोध असतात

प्रा. डॉ. मुकेश सरदार
कला, विज्ञान व वाणिज्य महाविद्यालय,
चिखलदरा. जि. अमरावती.४४४८०७

माणूस जेव्हापासून पृथ्वीवर जन्माला आला तेव्हापासून तो काही ना काही शोधत असतो. ही शोधक दृष्टी लहानपणापासूनच प्रत्येकाला प्राप्त झालेली असते. मात्र त्या दृष्टीला योग्य दिशा न दिल्यामुळे अनेकांना मरेपर्यंत काहीच शोधता येत नाही. आधुनिक युगात तंत्रज्ञानाला खूप महत्त्व प्राप्त झालेल्या आहे. या तंत्रज्ञानाच्या हव्यासा पायी खेडे आणि शहरे देखील आज उध्वस्त व्हायला निघालेली आहेत. आधुनिक जग हे भौतिक सुखाच्या मागे वेगाने धावतो आहे. आज जो दुनिया बरोबर धावत नाही तो संपून जातो. त्यामुळे समाजात निराशा, बेरोजगारी यासारखे ज्वलंत प्रश्न निर्माण झालेले आहेत. भौतिक सुख हे एक प्रकारचं शारीरिक सुख आहे. परंतु शरीराबरोबरच माणसाला मन देखील आहे. त्याला मानसिक भूक देखील आहे. आज मानवाची मानसिक़ भूक भागविण्यात विज्ञान असमर्थ ठरले हे निर्विवाद सत्य आहे. आकाशात आज सोयुझ अपोलोचे मिलन होत आहे. मात्र माणसा माणसातील मतभेद हे वाढतच आहे. एकमेकांची मने दुरावतच चालली आहेत. मानवाने सगळ्याच क्षेत्रात आज संशोधन केलेले आहे. तरीही आजचा आधुनिक माणूस दुःखी आहे. काकी मनाचे संशोधन मानवाला आजपर्यंत करताच आले नाही. एका सेकंदात पृथ्वीत किती बदल होतो याचे संशोधन झाले. मात्र ज्या मनामुळे माणूस दुःखी राहतो त्या मनाला सुखी करण्यासाठी कोणतेही तंत्रज्ञान आज उपलब्ध नाही. असे असले तरी बौद्ध साहित्यामध्ये मनाला चित्त संबोधून या चित्ताची वैज्ञानिक पद्धतीने चिरफाड केलेली आहे. जो व्यक्ती कुशल कर्म करेल तो सदैव सुखी राहतो. आणि जो व्यक्ती अकुशल कर्म करतो तो व्यक्ती सदैव दुःखी राहतो. हे सिद्धार्थ गौतम बुद्धांनी

सांगितलेले आहे. सिद्धार्थ गौतम बुद्धांची वाणी ही आर्यसत्यावर आधारित आहे. आर्य सत्य म्हणजे ज्यात खोट्याचा अजिबात लवलेश नाही असे. तुम्हाला जर निब्बाण, मोक्ष, मुक्ती प्राप्त करायचे असेल तर तुमच्या शरीराच्या आधारावरच ते प्राप्त करता येते. असे भगवान बुद्ध सांगतात.

जगामध्ये दोन प्रकारचे पर्यषण म्हणजे शोधआहेत.

१)आर्यपर्यक्षण २) अनार्य पर्यषण

एखादा मनुष्य स्वतः जन्मधर्मी असून जन्म धर्माचा शोध करीत असतो, जरा धर्माचा शोध करीत असतो,व्याधी धर्माचा शोध करीत असतो, मरण धर्माचा शोध करीत असतो, शोक धर्माचा शोध करीत असतो, मलधर्माचा शोध करीत असतो.

या संशोधनात तो गुंतून जाऊन वेडा होऊन, स्वतः जन्मधर्मी होऊन ,दुसऱ्या जन्म धर्मीयांचा शोध करीत असतो. याला अनार्य संशोधन असे म्हणतात.

तर आर्य संशोधन म्हणजे एखादा मनुष्य स्वतः जन्मधर्मी असून जन्म धर्मातील दृश्य परिणाम पाहून अजात (जन्म रहित)होऊन सर्वोत्तम निर्वाणाचा शोध करीत असतो.

स्वतः जराधर्मी, व्याधीधर्मी असून सुद्धा तो व्याधीरहित, जरारहित, मलरहित अशोक होऊन, योगक्षम निर्वाणाचा शोध करीत असतो. यातील वाईट परिणामांना पाहून निर्मळ होत असतो. हा सगळा गंभीर धम्म समजण्यास अवघड असल्यामुळे संम्यक संबुद्ध यांना असे वाटले की, हा धम्म सांगितल्यास लोकांना समजला नाही तर मला त्रासदायक पीडा देणारा होईल. पण पंडितांना समजू शकेल असा हा धर्म मी प्राप्त केला आहे.

सिद्धार्थ गौतम बुद्ध म्हणतात, असा समज माझा झाल्यामुळे माझे चित्त धर्मप्रचार करण्याकडे न झुकता अल्प उत्सुकतेकडे झुकले. तेव्हा ब्रह्मसहंमतीने माझ्या मनातील उदासीनता ओळखून विचार केला अरे! अरे!जगाचा नाश होईल जर तथागता चे चित्त धर्मप्रचाराकडे न चुकता उदासीन तिकडे झुकले तर जगाचा विनाश

होईल. असा विचार करून ज्याप्रमाणे एखादा बलवान मनुष्य प्रयत्न न करता पसरलेला हात झटकन जवळ घेतो किंवा जवळ असलेला हात झटकन पसरतो त्याचप्रमाणे ब्रह्मलोकांतून अंतर्धान होऊन तो माझ्यासमोर प्रकट झाला. नंतर सहंमपतीने ब्रह्माने उपरणे एका खांद्यावर करून, जिकडे मी होतो तिकडे हात जोडून विनंती केली. भंते भगवान धर्मोपदेश करा! सुगत !धर्मोपदेश करा! पुष्कळ प्राण्यांवर फक्त थोडाच मळ चढलेला आहे, धर्मवाक्य कानी न पडल्यामुळे त्यांचे नुकसान होत आहे .त्यांना उपदेश करा! धर्म समजणारे पण असतील! सहंपतीब्रह्मा पुढे असेही म्हणाला.

ह्या मगध देशात मलीन चित्त असलेल्या लोकांनी शोधलेला अशुद्ध धर्म पसरलेला आहे. म्हणजेच अनार्य पर्यषण निर्मळ मनाने जाणलेला असा हा तुमचा धर्म त्यांना ऐकवा! अमृताचे दार त्यांच्यासाठी खुले करा! एखादा मनुष्य पर्वताच्या शिखरावर जाऊन खालच्या लोकांच्याकडे पाहतो, त्याप्रमाणे हे सर्वज्ञ! धम्मप्रसादावर चढून आणि शोक विरहित होऊन तुम्ही या शोकात बुडालेल्या आणि जन्ममरणाने पराभूत झालेल्या लोकांकडे पहा !हे संग्रामात जिंकलेल्या वीरा !हे सार्थवाह !हे ऋणमुक्त पुरुषा! उठा !आणि लोकांमध्ये संचार करा! भगवान आता तुमच्या धर्माचा उपदेश करा ! त्यामुळे या जगात धर्म जाणणारे पुष्कळ तयार होतील.

तेव्हा सहंमपती ब्रह्मची भगवंतांनी धर्म उपदेश करण्याची विनंती मान्य केली. आणि पहिले धर्म प्रवर्तन सारनाथ येथे केले. त्यानंतर तेथे आंधळ्या झालेल्या लोकांत अमृतदुदुंभी वाजविली.

तथागत संम्यक संबुद्ध म्हणतात,

जो कोणी श्रमण किंवा ब्राह्मण काम गुणांनी बांधलेला नाही, सावध आहे, अलिप्त आहे, दृश्य परिणामांना पाहून बाहेर पडण्याची बुद्धी ठेवून, उपभोग करतो. त्याच्या बाबतीत समजले पाहिजे की, तो वाईट गोष्टीत पडलेला नाही. व्यसनात पडलेला नाही. पापाच्या इच्छेनुसार करणारा नाही. ज्याप्रमाणे भिक्खूंनो! जंगलातील मृग पाशराशीने न जखडता झोपावा? कारण काय तर तो मृग वाईट गोष्टीत पडलेला

नाही व्यसनात पडलेला नाही. शिकाऱ्याच्या इच्छेप्रमाणे करणारा नाही. शिकारी आल्यावर आपल्या इच्छेनुसार पळून जाऊ शकेल असे समजले पाहिजे. त्याप्रमाणे जो कोणी श्रमण किंवा ब्राह्मण पाच काम गुणांनी बांधलेला नाही, पापीच्या इच्छेनुसार करणारा नाही, ज्याप्रमाणे जंगलातील मृग वारा सुरू झाल्यावर निश्चिंत चालतो, निश्चिंत उभा राहतो, निश्चिंत बसतो, निश्चिंत पडतो, कारण काय तो शिकाऱ्याच्या आवाक्याबाहेर आहे. त्याप्रमाणे भिक्खूंनो प्रथम ध्यानाला प्राप्त करून भिखू विहरत असतो. म्हणून त्या भिखूच्या बाबतीत असे म्हटले जाते, त्याने माराला आंधळे केले आहे. माराच्या डोळ्याला मारून ,तो पापीच्या पुढून अंतर्धान पावला आहे. आणि भिखूंनो! तो भिखू द्वितीय ध्यानाला प्राप्त करून विरत असतो. भिखूनो म्हणून त्या भिखूच्या बाबतीत असे म्हटले जाते की, त्याने तृतीय ध्यान, चतुर्थ ध्यान ,आकाश आयतनध्यान, विज्ञानायतन ध्यान, अकिंचन्यायतन ध्यान, नवसंज्ञा-ना संज्ञायतन ध्यान संज्ञावेदित निरोधाला प्राप्त होऊन विहरतअसतो. प्रज्ञनेने पाहून त्याचे आश्रव नष्ट झालेले असतात. भिखूंनो अशा भिखू च्या बाबतीत म्हटल्या जाते पापीच्या पुढून अंतर्धान पावला. तो जगामध्ये पाशाचा पार झाला. तो निश्चिंत चालतो. निश्चिंत उभा राहतो. निश्चिंत बसतो. निश्चिंत झोपतो. कारण काय भिखूंनो !तो पापी माणसाच्या पोहोचण्याच्या बाहेर गेला. भगवान असे म्हणाले, समाधानी होऊन त्या भिक्खूंनी भगवंताच्या भाषणाचे अभिनंदन केले.

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