Rayat Shikshan Sanstha's

Dr. Patangrao Kadam Mahavidyalaya, Ramanandnagar (Burli)

Research Promotion Committee

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		comprehensive review on traditional uses, phytochemistry, pharmacology, and health-promoting activities	Research. 2022; 1–52. Impact Factor 6.38	0951-418X
30	Mr. Mane A B	Approaches for in vitro propagation and production of plumbagin in Plumbago spp.	Springer- Nature Based Journal Applied Microbiology and Biotechnology. Impact factor 5.467	ISSN: 0175-7598 (print); 1432-0614 (web)
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कहानीकार : मुंशी प्रेमचंद

डॉ॰ काकासा बापूसा भोसले
रयत शिक्षण संस्था का
डॉ॰ पतंगराव कदम महाविद्यालय
रामानदनगर (बुर्ली) तह-पलूस (सांगली) महाराष्ट्र

'मेरे ख्याल से प्रेमचंद का लेखन उन सभी लेखकों से अधिक प्रासंगिक है जो केवल रचनात्मक स्तर पर या तो क्रांतिकारी परिस्थितियों का संसार खड़ा करते हैं या देहभोग को ही मानवीय नियति मान लेते हैं।"

अपने काल के चिंतन और संवेदना को संप्रेषित करना ही सार्थक या प्रासंगिक माना जाता है। लेखक का अनुभव उसके समय और सामाजिक परिवेश से बनता है। अपने समय की समझ और चिंतन के साथ ही रूढ़ि परंपरा की जानकारी भी लेखक के लिए आवश्यक होती है। अनुभव और ज्ञान के इसी समीकरण से ही लेखक में कालातीत दृष्टि का जन्म होता है। ऐसा लेखन स्थायी और कालजयी होता है।

प्रेमचंद अपने समय की मानसिकता और पारंपारिक चिंतन बोध से जुड़े हुए प्रतीत होते हैं। इनका लेखन मूलत: ग्रामीण समाज के भीतर बनते-बिगड़ते हुए मानवीय संबंधों का लेखन है। मानवीय रिश्तों को निरंतर तोड़ने और आहत करने का कार्य विषम आर्थिक परिस्थितयाँ करती हैं। आर्थिक अभाव से पीड़ित व्यक्ति के लिए सारे नैतिक और सामाजिक मूल्य निरर्थक और अनावश्यक प्रतीत होते हैं।

प्रेमचंद विश्व के उन महान साहित्यकारों में हैं, जिन्होंने शोषित पददलित एवं अपमानित मेहनतकश और सामंती विलासिता जैसे आम लोगों को अपने लेखन का विषय बनाया है। विषयवस्तु के प्रति इनके समान समर्पित लेखक बहुत ही कम हुए हैं।

विश्व साहित्य के स्तर पर प्राय: यही दिखाई देता है कि अधिकांश उपन्यासकार और कहानीकार अपना विषय उच्चवर्ग तथा सांमती लोगों के बीच ही ढूँढते हैं, शायद मध्यवर्ग तक इसके नीचे उतरने का कष्ट कुछ ही साहित्यकार करते हैं उनमें प्रेमचंदजी का नाम शीर्षस्थ है। इसलिए अपनी कृतियों में जहाँ तक बन पड़ा है, प्रेमचंद ने इन प्रताड़ित मूक लोगों के दर्द को सशक्त वाणी देने का प्रयास किया है। जैसे उदाहरण के तौर पर निम्नलिखित कहानियाँ हैं–

'ठाकुर का कुआँ' कहानी बड़ी छोटी है। इससे छोटी दूसरी कहानी प्रेमचंद जी ने नहीं लिखी। केवल तीन पेज वाली कहानी। प्रभाव की दृष्टि से कहानी बेजोड़ और अप्रतिम है। कहानी केवल यह है कि जोखू एक अछूत है, बीमार है। प्यास लगने पर उसकी पत्नी गंगी उसे पानी देती है। लेकिन वह पानी पीने लायक नहीं हैं, बदबू आ रही है। जोखू के लाख मना करने पर भी गंगी ठाकुर के कुएँ से ताजा पानी लाने चली जाती है। जो कुआँ अछूतों को निषिद्ध है। रात के समय

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Elementary Education in Maharashtra

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1. Introduction : Education is one of the most important social infrastructural facilities for the development of human resources and essential for promoting the economic growth of the country. It is important in the sense that it is crucial input for empowering people with skills and knowledge and giving access to productive employment in future. Accessibility of educational facility is not only expected to enhance efficiency but also improve the overall quality of life of human being. Equitable and inclusive education is sustainable development goals for education.

The provision of universal primary education is an effective anti-poverty measures that promote equity. People are poor because they lack skill entrepreneurship. Article 45 of the constitution stipulates that the state shall endeavorto provide free and compulsory education for all children until they complete the age of 14 years within a period of ten years from the commencement of the constitution. However the task of providing basic education to all, with concrete plans of action gained greater momentum only after the national policy of education in 1986, revised in 1992 with the world declaration on education for all adopted in Jometin in 1990. Basic education, child care education, the elementary education, education to adolescents, adult education, gender equality and quality improvement have been the focus of international attention. These international developments within the country brought the need for recognizing basic education as fundamental right of every citizen on priority basis. The 86th Constitutional Amendment of 2002 led to inclusion of a new article 21-A in part III of the Indian constitution that made free and compulsory education to all children of 6 to 14 years of age. It is imperative to give good quality of elementary education to all children in the age group of 6 to 14 years. Policies and program in this direction are also necessary for achieving the goal of education under the Millennium Development Goals as well as need commitment under the National Common Minimum Programme for increasing public expenditure on education to 6 percent at the national level.

The Sarva Shiksha Abhiyan was launched toward the end of the Ninth Plan to achieve the goal of universalization of elementary education through guided by five parameters such as i) Universal Access ii) Universal Enrolment iii) Universal Retention iv) Universal Achievement and v) Equity. The aim of the programme was to provide elementary education to all children's in the 6 to 14 age group. It

Problems of Sugarcane Farmers of River Banks in Palus Tahsil, Maharashtra

Mr. Maske Satish Ashok
Assistant Professor
Dr. Khade Ashok Shrirang
Associate Professor & Head of Dept.
Ms. Madavi Asha Budharam
Dr. Patangrao Kadam Mahavidyalaya,
Ramanandnagar (Burli)

Introductions: Mainly since the establishment of Maharashtra, Sangli district is known as the leading district in sugarcane production. A large amount of sugarcane has been produced from alluvial soils along the banks of rivers in Sangli district. Co-operative sugar factories located in Sangli district depend on this sugarcane producer. Sugarcane growers are the primary source of raw material to the sugar factory. This is the second pillar of the sugar industry. The prosperity of the sugar industry depends on the regular and continuous supply of sugarcane during the harvest season. Although the farmers have a stake in the factory, they have many options to supply sugarcane for the mill. A farmer is always aware of the production and income of the farm, because they have invested heavily in sugarcane cultivation. The factory should maintain good relations with the farmers to achieve the highest target of sugar production. Sugarcane growers have some problems with sugar mills. This study focuses on the life and work of sugarcane farmers. He expects that first priority should be given to farmers. The factory should implement a welfare approach for the development of farmers.

Review of Literature:

1) Jha T.N. Viswanathan K.U. (1999), published an article entitled "Problem and Prospects of Agricultural Development in Bihar". In this paper he has observed the relation between irrigation and crop diversification in Bihar state. Formation of irrigation latent involves personal and public investment. As a natural consequence, the farmer will not only make good use of irrigation, but will also use it in agriculture, which increases farm income

2) Patil P.V. (2002), his thesis is on "Geographical Analysis of Agricultural Technology in Sangli district". He analyzes the changes in farm technology and technical equipment is inevitable as to how changes in agriculture are done.

3) S.T. Arote and Dr.S.M. Lawande (2011), studied the "Agricultural Problems and Prospects of Yeola Taluka". his emphasis on agriculture problems in Nashik district of Maharashtra and Prospectus in Yeola Taluka. They said that

अक्षर वाङ्मय

वर्ष तेरावे, पुरवणी अंक ४, खंड. २

फेब्रुवारी २०२३

मुख्य संपादक

डॉ. नानासाहेब सुर्यवंशी

आर. एन. आय. फॉर इंडिया नवी दिल्ली
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फेब्रुवारी २०२३

संपादक
डॉ. नानासाहेब सूर्यवंशी

कार्यकारी संपादक
डॉ. शिवाजीराव देशमुख

प्रकाशक : सौ. रेखाताई नानासाहेब सूर्यवंशी, प्रतीक प्रकाशन
'प्रणव' रुक्मिणी नगर, थोडगा रोड, अहमदपूर ४१३५१५

मुद्रक: श्री. जे प्रिंटिंग प्रा लिमिटेड १४१६ सदाशिव पेठ पुणे- ४११०३०

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भूमंडलीकरण और हिंदी साहित्य (कहानी विधा के विशेष संदर्भ में)

डॉ.नितीन हिंदुराव कुंभार
हिंदी विभाग, डॉ.पतंगराव कदम महाविद्यालय रामानंदनगर (बुर्ली), तह- पलूस, जि.सांगली (महाराष्ट्र)

शोध सार :-

भूमंडलीकरण यह 21 वीं सदी की नयी अवधारणा है। वैज्ञानिक प्रगति और सूचना क्रांति के परिणामस्वरूप संपूर्ण विश्व एक गाँव में बदल गया है। आज चारों ओर भूमंडलीकरण का बोलबाला है। कोई भी इससे अलग रहकर अपना विकास नही कर सकता। इस सर्वग्रासी शक्ति का मुकाबला हमारी भाषा और साहित्य भी कर रहा है। भूमंडलीकरण के कारण मानव जीवन में निर्माण हो रहे अनेक पहलुओं को हिंदी कहानियों में उजागर किया गया है। तकनीकी और संचार माध्यमों के विकास के कारण बेरोजगारी की समस्या बढ़ रही है। पारिवारिक संबंधों में दरार आ गयी है। प्रेम, आदर, अपनापन, विश्वास की दीवारें ढह गयी है उपभोक्तावादी संस्कृति के परिणामस्वरूप हमारे सांस्कृतिक मूल्यों पर प्रश्नचिहन निर्माण हुआ है। भूमंडलीकरण के कारण नए मूल्य स्थापित हो रहे है। भूमंडलीकरण ने महानगरों के साथ – साथ गाँवों की संरचना को भी बदल दिया है। भारत के अनेक गाँव भूमंडलीकरण की चपेट में आ गए हैं। अतः भूमंडलीकरण के कारण बदलते समाज जीवन का यथार्थ चित्रण हिंदी कहानियों में हुआ है।

बीज शब्द :- भूमंडलीकरण, तकनीकी, बेरोजगारी, पारिवारिक विघटन, सांस्कृतिक मूल्य, ग्रामीण जीवन

आलेख :-

आज का युग भूमंडलीकरण का युग है। 21वीं सदी विभिन्न आविष्कारों और उपलब्धियों के कारण सबसे तीव्र परिवर्तनों और संक्रमण वाली शताब्दी सिद्ध हो रही है। विज्ञान एवं तकनीकी के क्षेत्र में हो रही आशातीत वृद्धि के कारण पूरी दुनिया एक वैश्विक गाँव में परिवर्तित हो रही है। भौगोलिक दूर - दराज की दूरियां कम हो रहीं हैं। संपूर्ण विश्व को एक ग्राम में तब्दील करने कि इस प्रक्रिया को अंग्रेजी में 'Globalization'[1] ('ग्लोबलाइजेशन') कहा जाता है। अंग्रेजी के इस 'ग्लोबलाइजेशन' शब्द के लिए हिंदी में भूमंडलीकरण, वैश्वीकरण, जागतिकीकरण आदि पर्यायी शब्दों का प्रयोग किया जाता है। स्थूल रुप से इनका शाब्दिक अर्थ है - पूरे विश्व का एकीकरण। अर्थात बिना किसी बंधन के एक देश से दूसरे देश तक वस्तुगत उत्पादनों, विचारों, मूल्यों आदि का आपस में साझा व्यवहार एवं आदान - प्रदान करना है। वैश्वीकरण को परिभाषित करते हुए 'रघुवंशमणि' जी लिखते हैं कि - "वैश्वीकरण वस्तुतः उस एकरुपिता की प्रक्रिया से है, जिसके अंतर्गत वस्तुओं, सेवाओं, उत्पादन साधनों, कच्चे माल, वित्त, प्रौद्योगिकी आदि का बिना सरकारी नियंत्रण के देश की सीमाओं से परे सीधा प्रसार होता है"।[2] अतः कोई भी देश सबसे अलग रहकर अपना विकास नही कर सकता। भारत भी इस ग्लोबलाइजेशन के दौड में शामिल है।

भारतीय संस्कृति 'वसुधैव कुटुंबकम्' का संदेश देती है। वह विश्व को एक परिवार मानती है। इस मान्यता के पीछे - सभी भेद-भावों को भूलकर मनुष्य परस्पर बंधुभाव से व्यवहार कर सबके साथ अपनी उन्नति करे - यही सद्भावना छिपी है। वैश्वीकरण तथा भूमंडलीकरण के समर्थक भी यही कहतें हैं। उनके मतानुसार वैज्ञानिक प्रगति और सूचना क्रांति के परिणामस्वरूप संपूर्ण विश्व एक गाँव में बदल गया है। आज चारों ओर वैश्वीकरण का बोलबाला हो गया है। इस वैश्वीकरण, भूमंडलीकरण, उदारीकरण की आड़ में पूँजीवाद सर्वग्रासी तांडव कर रहा है। इस सर्वग्रासी शक्ति का मुकाबला हमारी भाषा और साहित्य भी कर रहा है। सारा समाज वैश्वीकरण की मजबूरी से दब-सा गया है। इसका प्रतिबिंब हिंदी साहित्य में विशेषतः कहानी विधा में यथार्थ रूप में दिखाई देता है।

भूमंडलीकरण का सीधा प्रभाव शिक्षा व्यवस्था पर हुआ है। नये तकनीकी और संचार माध्यमों के विकास के कारण बेरोजगारी तथा अस्थायी नौकरियों की समस्या बढ़ रही है। प्राचीन भारत में शिक्षा को एक संस्कार समझा जाता था। परंतु वर्तमान युग मे शिक्षा को व्यवसाय बनाया गया है। उसकी विडम्बना राजीव शर्मा की 'तजुर्बा' कहानी में दिखाई देती है। कहानी का नायक नरेंद्र एम. कॉम., बी. एड. उत्तीर्ण होकर नौकरी के लिए दर-दर भटक रहा है। एक जगह पर उसे नौवीं-दसवीं की कक्षा को गणित पढ़ाने का काम मिलता है। परंतु उसके प्राधानाचार्य उसके श्रम का शोषण करते हैं। "समय की मार तो पत्थर को भी गोल और चिकना बना देती है। यही नरेंद्र आज 5000/- रुपये पर हस्ताक्षर करके चुपचाप 3000/- रुपये जेब में डाल लेता था। शायद अपनी कमाई की आवाज अंदर के क्रांतिकारी विचारों का दमन कर चुकी थी या फिर विद्रोही तेवर यह सब छिन जाने के भय से कहीं दबे या दुबके रह जाते थे।"[3] भूमंडलीकरण के दौर में आज अस्थायी नौकरी करनेवालों की मजबूरी का फायदा उठाकर

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उनका शोषण करनेवाली व्यवस्था का यहाँ यथार्थ चित्रण हुआ है। 'भूमंडलीकरण के प्रभाव से घर - परिवार भी अछूते नहीं रहे। प्रेम, आदर, अपनापन, विश्वास की दीवारें ढह गयी है। विशेषतः परिवार में बुजुर्गों की ओर उपेक्षित तथा मजबूरी की दृष्टि से देखा जाने लगा। क्योंकि वैश्वीकरण के दौर में हर व्यक्ति की लाभ पर नजर रहती है। इस वृत्ति के कारण अपने ही घर में बुजुर्गों की उपेक्षा होती रहती है। राजीव शर्मा की 'सुपुत्र' कहानी में सेठ भागमल अपने तीनों बेटों को व्यवसाय सौंपकर अलग रहने लगते हैं। बहुएँ कभी-कभी फोन करके पूछताछ करती हैं, परंतु बेटे फोन तक नहीं करते हैं। इसलिए सेठ भागमल अपनी पत्नी के साथ रिक्षा में बैठकर बेटों से मिलने के लिए जाने लगते हैं। परंतु रास्ते में उनकी पत्नी कृष्णा बीमार हो जाती है और दो दिन के उपचार के बाद उसकी मृत्यु हो जाती है। तीनों बेटे पिता भागमल को हरिद्वार भेजना चाहते हैं। सेठ हरिद्वार जाने से मना करते हुए कहते हैं, "बेटा, इतनी दूर क्यों व्यवस्था कर रहे हो। उसी मकान में ही रहने दो। आखिर मरने के बाद मेरी शवयात्रा भी तो तुम लोग यही, इसी घर से ही तो निकालोगे। व्यर्थ ही हरिद्वार आने-जाने में तुम्हारा समय नष्ट होगा।"[4] इस प्रकार इस कहानी में व्यंग्य के साथ आज की पारिवारिक विघटन की सच्चाई स्वाभाविक ढंग से अभिव्यक्त की है।

भूमंडलीकरण और स्त्री विमर्श का हिंदी साहित्य में अपना अलग एवं महत्वपूर्ण स्थान रहा है। भूमंडलीकरण, बाजारीकरण, जागतिकीकरण, उपभोक्तावादी संस्कृति के परिणामस्वरूप नारी की स्थिति में काफी परिवर्तन आया है। नारी में आत्मविश्वास, चेतना, जागृति, आधिकार प्राप्ति के लिए संघर्ष आदि के साथ – साथ अंतर्जातीय विवाह, विवाहेत्तर अवैध यौन संबंध, आतंक और हत्या आदि घटनाओं का चित्रण हिंदी कहानी साहित्य में हुआ हैं। पाश्चात्य संस्कृति के अंधानुकरण के कारण हिंसा और सेक्स को बढावा मिल रहा है। अतः हमारे सांस्कृतिक मूल्यों पर प्रश्नचिहन निर्माण हुआ है। निर्मल वर्मा का कहानी साहित्य इन्हीं मूल्यों का दस्तावेज है।

'अंतर' कहानी की नायिका बिना विवाह किए अपने प्रेमी के साथ रहती है। उससे प्रेम करती है और गर्भवती हो जाती है। वह आधुनिक नारियों की तरह मुक्त और आजाद जीवन जीना चाहती है। वह एबोर्षन करवाने के लिए शहर में आई है। उससे मिलने नायक आता है, नायिका को कुछ चीजें देता है, किंतु उसके चले जाने पर वे चीजें बाहर फेंक देती है। दोनों के प्रेम संबंधों में दरार उत्पन्न हुई है। यहाँ पाश्चात्य संस्कृति के प्रभाव के कारण मुक्त प्रेम संबंधों का यथार्थ चित्रण हुआ है। यह भूमंडलीकरण का ही परिणाम कहा जा सकता है।

'पिता और प्रेमी' कहानी में नायिका विवाहोपरांत अपने प्रेमी से संबंध बनाए रखती है। कहानी में एक युवक और युवती बहुत दिनों के बाद अचानक मिलते है। दोनों के संवादों से बच्चे को मालूम होता है - "मुझे नहीं मालूम था, हम दुबारा मिलेंगे इस तरह। बच्चा चौंक गया। शायद माँ की हँसी सुनकर, क्योंकि उसने कभी उसे इस ढंग से हँसते नहीं देखा था। बहुत कम उम्र में भी बच्चे शायद अपने माँ के प्रेमियों को भाँप जाते है।... प्रेमियों को देखकर नहीं उनके प्रति अपनी माँ का रूख देखकर।" [5] संक्षेप में कहा जा सकता है कि एक ओर वैश्वीकरण ने नारियों के लिए कई दरवाजे खोल दिए। वह शिक्षा अर्जित कर रही है। आत्मनिर्भर बनती चली जा रही है। तो दूसरी ओर स्त्री-पुरूष भेद मिटकर मैत्री संबंध पनप रहे है। बॉय- फ्रेंड या गर्ल- फ्रेंड होना सभ्यता का लक्षण माना जा रहा है। लड़कियाँ मोहजाल में फँसती जा रही है। विवाहेत्तर संबंध को बढावा मिल रहा है। दांम्पत्य विघटन हो रहा है। वैश्वीकरण के कारण नए मूल्य स्थापित हो रहे है। वर्तमान काल में वैश्वीकरण के प्रभाव से बनते बिगडते इन सभी मूल्यों के दस्तावेज हिंदी कहानी में प्राप्त होते है जो नगरीय-महानगरीय स्त्रियों को सोचने के लिए मजबूर करते है।

भूमंडलीकरण यह 21 वीं सदी की नयी अवधारणा है। बीसवीं सदी के अंतिम दो दशक में इसकी नींव दिखाई देती है, परंतु हिंदी साहित्य में इसका प्रचलन आज की सदी में ज्यादा दिखाई देता है। आज देश में प्रत्येक राज्य, शहर, गाँव इस भूमंडलीकरण के परिप्रेक्ष्य में आया है। अजय तिवारी जी भूमंडलीकरण के बारे में कहते है कि "भूमंडलीकरण दो बड़ी घटनाओं का संयुक्त रूप है। एक चीज है सूचना और दूसरा बाजारवादी व्यवस्था।"[6] इन दो रूपों से ही भूमंडलीकरण का दिन-ब-दिन विस्तार होता दिखाई दे रहा है।

सूर्यनाथ सिंह जी ने भूमंडलीकरण और बाजारवाद के प्रभाव से गाँवों की बदलती संरचना को चित्रित किया है। सूर्यनाथ सिंह की कहानी 'जो है सो' में बदलते ग्रामीण जीवन की दास्ता है। बाजारवादी संस्कृति ने इस गाँव को तोड़ा है, गाँव की संस्कृति मिटती जा रही है। गाँव टूट रहे हैं, बिखर रहे हैं। लोग शहर की तरफ भाग रहे हैं। गाँवों में औद्योगिक विकास हो रहा है। विदेशी कंपनियाँ गाँवों की तरफ अपना आकर्षण बनायी हुई है। गाँव उनका स्वागत कर रहे हैं। क्योंकि खेती में न किसानों को मुनाफा मिल

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रहा है और न उसमें उपज बढ़ रही है। ऐसे में किसानों के बेटे अपने पुरखों की जमीन बेच रहे है और बूढ़े जमीन बेचने को तैयार नहीं हैं। जमीन उनके मान-सम्मान की निशानी है। वे कहते हैं कि "अरे, ई जमीनिया हैं तब तक मान-सम्मान, अभिमान है, खाके फुटानी छाक रहे हो। जिस दिन नहीं रहेगी, उस दिन कुक्कुर सियार भी पूछने नहीं आएगा।"7 प्रस्तुत कहानी में दो पीढ़ियों के बीच में मतभिन्नता दिखायी है। परंतु नवयुवक, जो बेरोजगार है, जिनके हाथों को काम नहीं है वे नौकरी, व्यवसाय तथा बनियेगिरी के सपने देखते हैं। वे कहते हैं कि "साला, बिजनेस सेंटर खुलेगा तो इस जिले का भाग जाग जाएगा। दिल्ली, बम्बई, बंगलोर जाने का कौनो जरूरते नहीं। दस हजार की नौकरी के लिए ससुर खेत-बारी बेच के घूस देने का जुगत भिडाते रहे.....।"4 युवावर्ग सपने देख रहा है कि कोई रोजी-रोटी का काम मिले। कहानीकार ने युवा पीढ़ी की मानसिकता तथा संवेदनशून्यता का बड़े ही मार्मिकता के साथ चित्रण किया है। ऐसे अनेक गाँव भारत में हैं जो भूमंडलीकरण के दायरे में आ गए हैं। 'नौगांवा' इन गाँवों का प्रतिनिधित्व करता है।

निष्कर्ष :- निष्कर्ष रूप में कहा जा सकता है कि आज भूमंडलीकरण के बढ़ते प्रभाव ने पूरे विश्व को एक कमरे में बंद कर दिया है। इस भूमंडलीकरण ने पुरानी संस्कृति और नई संस्कृति के बीच द्वंद्व निर्माण किया है। भूमंडलीकरण के प्रभाव से सारा समाज दब-सा गया है। हमारी भाषा और साहित्य भी इससे अछूते नहीं रहे हैं। तकनीकी और औद्योगिक क्षेत्र में हो रही आशातीत वृद्धि के कारण समाज में बेरोजगारी की समस्या बढ़ रही है। पाश्यात्य संस्कृति के अंधानुकरण के कारण पारिवारीक संबंधों में दरार, अंतर्जातीय विवाह, विवाहेत्तर अवैध यौन संबंध आदि को बढावा मिलने से हमारे सांस्कृतिक मूल्यों पर प्रश्नचिहन निर्माण हुआ है। भूमंडलीकरण यह भूत ग्रामीण क्षेत्रों पर भी हावी होता दिखाई दे रहा है। विकास मार्ग पर दौड़ लगाकर महानगर गाँव तक पहुँच गया है। भूमंडलीकरण के प्रभाव से गाँवों का नया यथार्थ अनुभूति के द्वारा अभिव्यक्त हो रहा है। हिंदी कहानी साहित्य में इसका यथार्थ चित्रण परिलक्षित होता है।

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हिंदी दलित कहानियों में दलित परिवेश का चित्रण

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तह-पलूस (सांगली) महाराष्ट्र

हिंदी दलित कहानी सशक्त रूप में विकसित हुई है। दलित रचनाकारों ने अपने अनुभवों एवं जातिगत उत्पीड़न को कहानी के माध्यम से प्रस्तुत किया है। डॉ॰ बाबासाहेब अंबेडकर के क्रांतिकारी विचारों से प्रेरित रचनाकारों ने उनके विचार अपनी कहानियों के माध्यम से सामान्यजनों तक पहुँचाए। दलितों की दासता, अपमान, शोषण के विरुद्ध विद्रोह करती हुई कई दलित कहानियाँ समता पर आधारित नए समाज की निर्मिति के मूल उद्देश्य से रची गई हैं।

दलित कहानियाँ दलितों के परिवेश से जुड़ी हुई हैं। हिंदी दलित कहानियों में प्रमुख रूप से उत्तर भारत के दलितों का परिवेश अंकित है। चूँकि आधुनिकता के दौर में दलित ग्रामीण सीमा लाँघकर शहरों में भी बस गए हैं, ये कहानियाँ दलितों के ग्रामीण परिवेश तक ही सीमित न रहते हुए शहरी परिवेश को भी समाहित करती हैं।

ग्रामीण परिवेश

डॉ॰ अंबेडकर ने गाँवों को गणतंत्र की अवधारणा का शत्रु माना था। शोषक, पूँजीवादी प्रवृत्ति भारत के गाँवों में ही पनपती है और गाँव के गरीब, अशिक्षित दलित उसका शिकार बन जाते हैं। भारत के हर गाँव में दलितों की अलग बस्ती का रिवाज है। यह दलितों की बस्ती गाँव से दूर होती है। दलितों के उद्धार के लिए इस प्रकार की अलग बस्तियों ही मिटाने की आवश्यकता डॉ॰ अंबेडकर ने व्यक्त की थी। उनके अनुसार, 'गाँव-गाँव के महारवाड़े (दलितों की बस्ती) नष्ट करने चाहिए। हर महारवाड़ा लोगों का बंदीगृह और गुलामघर है। वह गुलामी का द्योतक है।'[1]

हिंदी दलित कहानियों में ग्रामीण परिवेश का चित्रण प्राप्त होता है। ग्रामीण दलितों को जिन समस्याओं, भेदभावपूर्ण व्यवहार, शोषण का सामना करना पड़ता है उनका चित्रण कहानियों में प्राप्त होता है। मोहनदास नैमिशराय की कहानी 'आवाजें' में उत्तर भारत के गाँव के परिवेश का चित्रण मिलता है। गाँव से अलग बस्ती में रहनेवाले दलितों की व्यथा वेदना उन्होंने व्यक्त की है। लेखक ने गाँव की दलित बस्ती का चित्रण करते हुए लिखा है, 'दूर गाँव के पूर्वी छोर पर मेहतरों का एक टोला था। जिसमें बीस-तीस परिवार शहर भर की जूठन खा-खाकर अपना पेट भरते थे। वहाँ मकान के नाम पर कुछ फूस की झोपड़ियाँ तथा आँगन के रूप में गोबर से लिपे-पुते जमीन के छोटे-बड़े टुकड़े थे।'[2]

ग्रामीण प्रदेश में कड़ी मेहनत मजदूरी करने पर भी दलितों को दो वक्त की रोटी नसीब नहीं होती। उनका अभावपूर्ण जीवन एवं ग्रामीण दलितों का सवर्णों द्वारा होनेवाला शोषण दलित कहानियों में चित्रित हुआ है। ओमप्रकाश वाल्मीकि की कहानी 'बैल की खाल' में मरे हुए जानवरों

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CONTENT

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हिंदी उपन्यास साहित्य में पर्यावरणीय चेतना

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शोध सार :-

विश्व में भारतीय संस्कृति का अपना एक अलग - सा महत्व रहा है ।भारतीय संस्कृति ने हमेशा मानव कल्याण का ही संदेश दिया है । प्राकृतिक संपदा के संरक्षण का भी वह हमेशा संदेश देती रही है । अनादिकाल से हमारे यहाँ के ऋषि मुनियों तथा महामानवों ने प्राकृतिक संपदा - जल, थल, वन की रक्षा का संदेश देकर उनके संरक्षण के प्रति मनुष्य को सजग किया है ।प्रकृति और मनुष्य का अटूट नाता जोड़ने की कोशिश की है, इनके अनुसार प्रकृति से उसका प्रेम और साहचर्य ही मनुष्य को पर्यावरण प्रदूषण से बचा सकता है, परंतु आजकाल वैज्ञानिक तथा तकनीकी आविष्कार के कारण एक ओर औद्योगिकीकरण, शहरीकरणका विकास हो रहा है तो दूसरी ओर जनसंख्या विस्फ़ोट आदि के कारण हमारे देश के वन और वनों की अमूल्य संपत्ति का दिनोंदिन ह्रास हो रहा है, स्वच्छ व शुद्ध प्राकृतिक पर्यावरण दूषित होने लगा है । जिसके अनेकानेक कारण है । इस संदर्भ में सुमेष, ए.एस, लिखते है कि - 'प्राकृतिक संसाधनों के अत्यधिक शोषण, जनसंख्या में वृद्धि और अनियंत्रित औद्योगिकीकरण और नियोजित कोंक्रीट भवनों का निर्माण, पर्यावरण असंगत विकास योजनाएं, यातायात के साधनों की संख्या में वृद्धि, खनन द्वारा खनिजों की प्राप्ति, जंगलों के कटाव' आदि के कारण पर्यावरण प्रदूषण तथा पारिस्थितिक असंतुलन की समस्या सामने आती है ।[1]इसका चित्रण हिंदी उपन्यास साहित्य में भी किया गया है।

हिंदी की लोकप्रिय लेखिका कुसुम कुमार के द्वारा लिखित 'मीठी नीम' नामक उपन्यास भी इस दृष्टि से एक सशक्त रचना है। 'मीठी नीम' पर्यावरणीय चिंताओं और पर्यावरण संरक्षण की जन जागृति पर आधारित 21वीं सदी का अत्यधिक महत्त्वपूर्ण उपन्यास है। लेखिका कुसुम कुमार इस उपन्यास में कई प्रश्नों एवं परिस्थितियों से हमारा सामना करवाती है और हर एककी वकालत में प्रतिबद्ध रहने वाली पात्रा ओमना के माध्यम से पर्यावरण संरक्षण की चेतना जगवाती हुई दिखाई देती है।

बीज शब्द :-

संस्कृति, प्राकृतिक पर्यावरण, संसाधन, संरक्षण, असन्तुलन, जनजागृति प्रकृति, हरियाली

आलेख :-

आज विश्व के सामने पर्यावरण के असंतुलन की समस्या अपना एक विकराल रूप धारण किए हुई है ।हिंदी उपन्यासों में भी पर्यावरण की समस्याजैसा विषय अत्यंत ज्वलंत प्रश्न बनकर उभर रहा है।कई लेखक और लेखिकाओं ने पर्यावरणीय समस्या को एक गंभीर विषय के रूप में चित्रित किया है और अपने साहित्य में प्राकृतिक संपदा जल, जंगल और जमीन के असीमित हनन और उससे निर्माण होने वाली समस्याओं का बखूबी - से यथार्थ चित्रण किया है। साथ ही समाज में यह चेतना जगाने की कोशिश की है कि जब तक मानव एवं प्राकृतिक पर्यावरण में पारस्पारिक आदान-प्रदान परक

सामंजस्य नहीं होता तब तक विकास की गति अवरुद्ध ही रहेगी और यूं ही हमारे प्राकृतिक संसाधनों का ह्रास होता रहेगा और इसके लिए स्वयं मानव जाति को जिम्मेदारीउठाने पड़ेगी । पर्यावरण की समस्या को चित्रित करनेवाले ऐसे कई बेहतरीन उपन्यास हिंदी में लिखे गए हैं जिनमें पर्यावरण के संरक्षक को मूर्त रूप में दिया गया है । कुसुम कुमार का 'मीठी नीम' उपन्यास एक ऐसी ही सशक्त कृति है । जिसमें मानवीय क्रियाकलापों के कारण होने वाले प्रकृति परिवर्तनों को लक्षित किया गया है और इससे पर्यावरण के होनेवाले असंतुलन को भी अधोरेखित किया है ।जैसे - ऋतुएं भी समय से नहीं आतीं, धरती से हरियाली का स्थान सीमेंट - ईंट की बनी पक्की सड़कों और बहुमंजिली इमारतों ने लिया है। इसी की ओर संकेत करते हुए लेखिका ने 'मीठी नीम' उपन्यास के माध्यम से पृथ्वी को पुनः हरा भरा बनाने का आवाहन किया है ।

'मीठी नीम' उपन्यास का प्रारंभ ओमना के हरित प्रेम से होता है, नये - नये प्रयोग करने की जिद, कल्पना की उड़ान और आत्मविश्वास के बल पर वह अपने आसपास हरे को प्रसारित करने के निरन्तर नए नए प्रयास करती रहती है। उसका अटूट विश्वास है कि उसका हरे को विस्तारित करने का यह सपना कभी ना कभी यथार्थ में परिवर्तित होगा ही। चूँकि ओमना निरन्तर हरित हरे की ओर अग्रसर है इसलिए लेखिका ओमना के माध्यम से यही संदेश जन - जन तक प्रेषित करना चाहती है कि हमें भी अपना मन हरे की ओर ले जाना चाहिए। हरा रंग स्फूर्ति - ताज़गी का प्रतीक है, ऊर्जा का प्रतीक है, सुखमय जीवन का प्रतीक है और यही हरा रंग हरियाली यानी हरी भरी धरा में विद्यमान है।अर्थात यदि सर्वत्र हरियाली, हरित हरा फैला होगा तो जीवन भी ऊर्जावान, स्फूर्ति, ताज़गी से पूर्ण होगा और इसी जीवन को सुरक्षित रखने के लिए हरे को सुरक्षित रखना मनुष्य का अनिवार्य आदि कर्तव्य है। सम्पूर्ण संसार में प्रकृति ही ऐसी है जो न ऊब पैदा करती है न ही थकाती है। उपन्यास में ओमना यही संदेश देती है कि "मन को कहीं न कहीं रमना होता है। हरे में रमे, तो मनुष्य की तुलना में कहीं वरद।"[2]मनुष्य में तो एक समय के बाद विरक्ति - थकान निर्माण हो सकती है परंतु प्रकृति हमें सदा ही प्रेरणा, उर्जा, स्फूर्ति - ताज़गी प्रदान करती है। प्रकृति हमें हमारी क्षमताओं से परिचित कराती है और वैसे भी 'हम ऐसी दुनिया में रहते हैं जिसमें प्राकृतिक संसाधन सीमित हैं। जल, वायु, खनिज, तेल, घास के मैदान, सागर, कृषि और मवेशियों से मिलने वाली सभी वस्तुएं - ये सभी हमारी जीवन रक्षक व्यवस्थाओं के अंग हैं। जैसे जैसे हमारी जनसंख्या बढ़ेगी और हममें से हर एक व्यक्ति द्वारा संसाधनों का उपयोग भी बढ़ेगा, तो पृथ्वी के संसाधनों का भंडार निश्चित रूप से कम होगा।''[3] ऐसी स्थिति में आवश्यकता है संसाधनों के अमर्याद प्रयोग पर अंकुशलगाने की और साथ ही पर्यावरण संरक्षण के प्रति समाज में चेतना जगाकर हमें अपनी प्रतिबद्धता - जिम्मेदारियाँ भी सुनिश्चित करनी होगी।जिससे हमारा ही नहीं बल्कि आने वाली पीढ़ियों के जीवन भी सुरक्षित रह सकेंगे। जिसे उपन्यास की प्रकृति प्रेमी पात्रा ओमना बखूबी से निभाती हुई दिखाई देती है। उसे दादी बनने की खुशी है लेकिन अपने पौधों को छोड़कर वह बेटे के साथ न जाने का निश्चय करती है। यही प्रकृति प्रेम ओमना को एक ऊँचे स्थान पर प्रतिष्ठित करता है । जिससे प्रेरणा पाकर एक नहीं अनेक ओमना बन सकती है। जैसे उपन्यास में प्रीति और शांता बनी हुई दिखाई देती है ।

आजकल मनुष्य अपने सुखमय जीवन के लिए, शहरीकरण के लिए अनेक संसाधनों का कुछ प्रयोग तो अवश्य ही कर रहा है । जैसे हमारे देश की राजधानी दिल्ली को ही लें, दिल्ली में मेट्रो सेवा शुरू हुई, सभी दिल्लीवासियों के लिए यह राहत की बात थी, लेकिन लेखिका की दृष्टि प्रकृति की ओर भी रही है। एक ओर ओमना के भीतर गाड़ी में बैठने की उत्सुकता है तो दूसरी ओर जिन रास्तों से होकर मेट्रो गुजरी है वह भी उसकी दृष्टि से ओझल नहीं रह सका है। यहाँ कुसुम कुमार लिखे बिना नहीं रह पाती कि "इस गाड़ी की सफलता की पृष्ठभूमि में शहर के कुछ वयोवृद्ध वृक्षों का योगदान। यह सच्चाई सरकारों, नौकरशाहों से अधिक पैदल पथिक जानते।"[4] चाहे मैट्रो का विस्तार हो अथवा सीमेंट की सड़कें - इमारतें बनानी हों, परंतु यह सच है कि कुछ पाने के लिए अवश्य ही कुछ खोना

पड़ता है, यही कारण है कि बीच में पड़ने वाले हरे भरे, छोटे बड़े वृक्ष तो काट ही दिए जाते हैं। दिल्ली के विकास की गति को देखकर ओमना कहती है "दिल्ली नाम की राजधानी, जो निखालिस पत्थर सीमेंट का जंगल, जहाँ किन्हीं जटाधारी वृक्षों की बलि सिर्फ इसलिए चढ़ाई जाती : रोड़ी पत्थर, तारकोल की सड़कों, पुलों को विस्तार देना है।"[5] जब भौतिक विकास की गति में तीव्रता से वृद्धि होने लगी तो समझ लेना चाहिए कि प्राकृतिक संसाधन भी तेजी से घटने लगेंगे । मानवीय क्रियाकलापों से हमारे पर्यावरण का अधिकाधिक ह्रास हो रहा है। विज्ञान के क्षेत्र में असीमित प्रगति तथा नए आविष्कारों की स्पर्धा के कारण आज का मानव प्रकृति पर पूर्णतया विजय प्राप्त कर लेना चाहता है। इस कारण प्रकृति का संतुलन बिगड़ गया है। वैज्ञानिक उपलब्धियों से मानव प्राकृतिक संतुलन को उपेक्षा की दृष्टि से देख रहा है तो दूसरी ओर धरती पर जनसंख्या की निरन्तर वृद्धि, औद्योगिकीकरण एवं शहरीकरण की तीव्र गति से प्रकृति के हरे भरे क्षेत्रों को समाप्त किया जा रहा है। उपन्यास में भी लेखिका जगह - जगह टिप्पणी करती चलती है कि फलां पुल बनाने के लिए एक लाख पेड़ काट दिए गए या मेट्रो के लिए दस हज़ार वृक्षों की बलि चढ़ा दी गयी। विकास बनाम विनाश यहीं से शुरू होता है, विकास के लिए प्रकृति का विनाश स्वयं ही आरम्भ हो गया है। ओमना का चिंतित होना जायज़ है, वह सोचती है कि "जाने अनजाने, विकास की प्रत्येक ईंट, हरियाली से बदला लिए बिना क्यों न रुकती, जानने की इच्छा होती।"[6] यही कारण है कि ओमना अकेली पर्यावरण संरक्षण की ओर कदम बढ़ा चुकी है और दूसरों को भी प्रेरित करती है कि ज़्यादा से ज़्यादा वृक्ष रोपो, पौधे लगाओ, उसे ऐसी लगन है कि हरे के प्रति कि जहाँ धूप का एक टुकड़ा, या आठ इंच जगह भी देखती है वहीं एक पौधा रोप देती है। 'जिस तरह इलाज से बेहतर विकल्प उसकी रोकथाम होती है ठीक उसी तरह पर्यावरण को हानि पहुँचाने के बाद उसकी भरपाई करने की तुलना में पर्यावरण का संरक्षण आर्थिक दृष्टि से अधिक व्यवहारिक है।'[7] जिससे प्रकृति को संबल प्राप्त हो सके और हमें जीवन मिल सके। 'मीठी नीम' की ओमना निडर, साहसी और प्रकृति प्रेमी महिला है जो न केवल अपने पेड़ पौधों से लगाव रखती है बल्कि पूरी जी जान से उनकी रक्षा भी करती है। मानवीय क्रियाकलापों के कारण पिछले कई वर्षों से पारिस्थितिक तंत्र में परिवर्तन हुआ है, उसका सीधा प्रभाव पर्यावरण पर भी हो रहा है, पारिस्थितिक असंतुलन के कारण मौसम में किस तरह परिवर्तन हुए हैं और निरन्तर हो रहे हैं यह किसी से छिपा नहीं है। मौसम पर अब मौसम विभाग का नियंत्रण नहीं रहा है, प्रतिवर्ष यही इच्छा होती है कि मानसून समय से आये, पानी सही मात्रा में बरसे, जाड़ा, गर्मी सभी उचित मात्रा में हों, लेकिन यह इच्छा पिछले कई वर्षों से पूरी नहीं हो पा रही है या कहें अब आशाओं में बदलती जा रही है। सर्दी में ठंड का अहसास नहीं होता, गर्मी में अति गर्मी और वर्षा में कभी बेहिसाब बारिश या उम्मीदों पर ही पानी फिरा देती है, बाढ़, सूखा, भूस्खलन जैसी प्राकृतिक आपदाएं आम बात हो चली हैं, पूरा उपन्यास ही इन घटनाओं को केंद्रित करके लिखा गया है। ओमना कहती है "आज सात दिसंबर, ठंड का नामोनिशान नहीं... जाड़ा ही क्यों, गर्मी, वर्षा, वसंत सभी ऋतुएँ हमारे हाथ से जाती रहीं। हम नियम तोड़ते गए क्रुद्ध प्रकृति हमारी उम्मीदों पर पानी फेरती।समय पर कोई ऋतु साथ न देती। विशेषज्ञ कारण जानते निदान नहीं।"[8]आधुनिक सुविधाभोगी जीवन शैली ने पर्यावरण पर बहुत गहरा प्रभाव डाला है जिसके कारण न केवल प्रकृति से हरे की विदाई हो रही है बल्कि मौसम भी साथ नहीं दे रहे। विशेषज्ञ कारण जाने न जाने लेकिन ओमना बखूबी जानती है। वह कहती है "और दौड़ाओ सड़कों पर बड़ी बड़ी गाड़ियां और बनाओ सौ - सौ मंजिला इमारतें, उसी का नतीजा है यह।"[9] जिस तरह की परिस्थितियां आज के समय में उत्पन्न हुई हैं जहां सब यंत्रवत हो जीवन की आपाधापी में व्यस्त हैं वहां प्रकृति की वकालत करने वाली ओमना निडर हो खड़ी है। एक समय ऐसा भी आता है जब ओमना वोट न देने का निश्चय करती है क्योंकि उसे लगता है वोट देने से बेहतर है जमीन में एक वृक्ष रोप देगी। ऐसा प्रतीत होता है कि ओमना राजनीति को समझ चुकी है। एक वोट से वह अपने मन का प्रतिनिधि नहीं चुनना चाहती वह नई तरह से लोकतंत्र को मजबूत करना चाहती है

क्योंकि उसका मानना है कि "पानी और हरियाली का निजाम देश के निजाम से कहीं बेहतर। बेहतर मिट्टी, पानी, बीज और दो चार ढीठ धरती के पक्ष में बोलते। देश का निजाम डेंगू, मलेरिया, पानी के गड्ढों को स्वायत्तता के झोले में डाल, किन्हीं बड़े प्रश्नों की ओर मुड़ जाता।"[10] 'मीठी नीम' उपन्यास में लेखिका की दृष्टि काष्ठ चोरी की तरफ भी गयी है। मतिराम के माध्यम से बेशक यह छोटे स्तर से शुरू हुई, रागमाला परिसर से नए पौधों की चोरियों से लेकिन मतिराम कुछ समय में ही इतना धन अर्जित कर लेता है जैसे वह कोई धन्ना सेठ हो। यही छोटी - छोटी चोरियां बड़े स्तर तक चली जातीं हैं और वनों का अवैध कटान शुरू होता है। उपन्यास में भले ही यह सीमित स्तर पर दिखाया गया हो। स्कूल में हरा भरा वृक्ष रातों रात गिर जाता है और किसी को खबर तक नहीं लगती और अगली सुबह उसे इतनी जल्दी उठाया जाता है जैसे मरे हाथी का मोल जीवित से कहीं अधिक होता है।

कुसुम कुमार उपन्यास में अंत तक मुख्य पात्रा ओमना के माध्यम से हरियाली का प्रसार करने में अग्रसर दिखाई देती हैं। हरित हरा का यह संकल्प जिस तरह पात्र ओमना ने लिया, लेखिका का उद्देश्य इसे प्रत्येक व्यक्ति के हृदय में उजाकर करना है। उपन्यास में लेखिका ने पर्यावरणीय समस्याओं को यथार्थ रूप में चित्रित कर पर्यावरण संतुलन के प्रति मनुष्य को सचेत किया है I

निष्कर्ष

कुसुम कुमार के द्वारा लिखित 'मीठी नीम' नामकउपन्यास में केवल समस्याओं को ही चित्रित नहीं किया गया है बल्कि कुछ हद तक उनका समाधान भी देने का प्रयास किया है। ओमना जहाँ रहती है यानी रागमाला परिसर, उसकी साठ प्रतिशत भूमि हरियाली के लिए छोड़ दी गयी है। हरियाली की दृष्टि से ऐसा करने वाला कोई पर्यावरण प्रेमी ही होगा जिसे देश की आम जनता के स्वास्थ्य की भी उतनी ही चिंता हुई होगी जितनी खास लोगों की। इसी तरह यदि सबकी सोच परिवर्तित हो जाये, अपने आसपास हरे - भरे वृक्षों के लिए स्थान बनाये जाने लगें। इसके साथ ही आधुनिक तकनीक का प्रयोग सीमित मात्रा में ही किया जाए क्योंकि सभी एक साथ एयरकंडीशनर चलाने लगें तो धरती का क्या शहर का तापमान कहाँ से कहाँ पहुँच जाएगा। इसलिए जितना आवश्यक हो उतना ही प्रयोग करना चाहिए। यह पारिस्थितिक असंतुलन से उत्पन्न प्रभावों को यथार्थ रूप में चित्रित करने वाला ऐसा अनोखा उपन्यास है जो न केवल इस असंतुलन को ही रेखांकित करता है बल्कि यह परिस्थितियां निर्मित ही क्यों हुईं इस ओर भी इशारा करता है। 'मीठी नीम' पर्यावरणीय चिंताओ से रूबरू कराते हुए पर्यावरण संरक्षण की बेजोड़ कृति है, जिसमें यह निहित है कि पृथ्वी के गुर्दे सही सलामत रहेंगे तभी हमारा जीवन बचा रह सकता है इसलिए हरियाली को सेवा और सुकृत समझना चाहिए उसे मुसीबत की तरह नहीं देखना चाहिए। 'मीठी नीम' पर्यावरण पर चिंतन करते हुए एक ऐसे सशक्त उपन्यास के रूप में हमारे सामने आता है जो शरीर के घाव दिखाकर उसके उपचार के रूप में व्याख्यायित होता। घाव यह है कि पारिस्थितिक असंतुलन निरन्तर बढ़ रहा है और इसका उपचार यह होगा कि प्रकृति, पर्यावरण को बचाने का जिम्मा उठा लिया जाए। जब तक घाव से होने वाली समस्याओं को नहीं बताया जाएगा तब तक व्यक्ति घाव ठीक करने का सोचेगा ही नहीं। उसके मन में कहीं न कहीं यह भी आ सकता है कि शायद यह घाव स्वयं ही ठीक हो जाये। ऐसे में आवश्यकता होती है जागरूकता की जिसका बीड़ा ओमना जैसी स्त्रियां उठाती हैं।

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Effect of bath temperature on the characteristics of Zinc Oxide

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Introduction : From existing various nanoforms of ZnO, nanorod is such a morphology that has received a great deal of attention in recent years, because of its unique optoelectronic, mechanical, magnetic and chemical properties provide various potential applications [1]. Zinc oxide (ZnO) possesses variety of nanostructures and it is the next most important material after carbon nanotubes [2]. Various chemical and physical deposition techniques have reportedly created an oriented structure of ZnO nanorods with average diameters typically ranging over an order of magnitude from 20 to 200 nm. For instance, catalytic growth via the liquid-solid-vapor epitaxy (VLSE) mechanism [3], metal-organic chemical vapor deposition (MOCVD) [4], pulsed laser deposition (PLD) [5] and epitaxial electrodeposition [6] have been particularly successful in creating highly oriented arrays of nanorods of ZnO. Out of these, Chemical Bath Deposition is a soft chemical method to deposit ZnO nanforms. However the coating of a substrate with nanosized ZnO seeds [7] or making use of templates [8] are the prerequisite conditions for the growth of vertically aligned ZnO nanorods.

In the present work, we are particularly successful in creating vertically aligned ZnO nanorod arrays by varying bath temperature. The strategy to design nanostructured thin film is entirely based on a wet chemical, bottom up approach; such an approach does not require any template, membrane, surfactant or applied external field to create nanoparticles or to control their orientation.

Experimental Details : An aqueous solution of 0.08 M Zn $(NO_3)_2$ was prepared, and to this solution aqueous NH_3 solution was added under constant stirring to maintain the Ph of the solution. A white precipitate was initially observed, which subsequently dissolved upon further addition of NH_3 solution. The solution was maintained at a pH -10.30 by addition of excess NH_3 solution. A pre-cleaned glass substrate was immersed and placed vertically in the solution. The bath temperature was 60°C, 70°C, 80°C and 90°C. The substrates, with the deposited ZnO nanorods, were thoroughly washed with deionized water to eliminate residual salts [9]. These films were annealed with variation in temperature from 200ºC–300ºC for 2 h and used for the further characterization. A Philips Japan MPD 1880

X-ray powder diffractometer was employed to study the crystal structure of the films. Surface morphology of the films was examined by scanning electron microscopy, SEM (JEOL, 15 kV). A Shimadzu double beam spectrophotometer was employed for obtaining transmittance in the wavelength range of 350–900 nm and to evaluate the direct band gap energies.

Results and Discussion : In chemical method, the small degree of supersaturation causes the heterogeneous nucleation of the metal oxide on the substrates [10]. For Zn^{2+} aqueous solution, the necessary condition for the formation of precipitation is the establishment of ion product higher than solubility product of Zn $(OH)_2$. The supersaturation can be controlled by optimizing the preparative parameters such as bath temperature, pH and concentration of resultant solution, to get nanocrystalline thin films. For the depositon ZnO, the mechanism of ZnO film formation can be elucidated as follows: Zn $(NO_3)_2$ was used as a source of Zn^{2+} ions. When ammonia was added to it, white precipitate of $Zn(OH)_2$ was occurred, further addition of ammonia resulted in to dissolution of $Zn(OH)_2$ in to the solution and formation of zincate ($[Zn(NH_3)_4]^{2+}$). The thermal decomposition of $[Zn(NH_3)_4]^{2+}$ releases ions of Zn^{2+} ions reacts with OH^- in the solution and results in the formation of $Zn(OH)_2$ or ZnO particles. As a result, the growth along the (002) plane has faster growth rate than that along other directions. This polarity causes the (002) face of the crystal either positively or negatively charged. In either case, surface will attract ions of opposite charges (O^{2-} or Zn^{2+}) to it, and this new surface covered with ions will in turn attract ions with opposite charges to cover the surface next and thereby reacting to form ZnO nanorods [11].

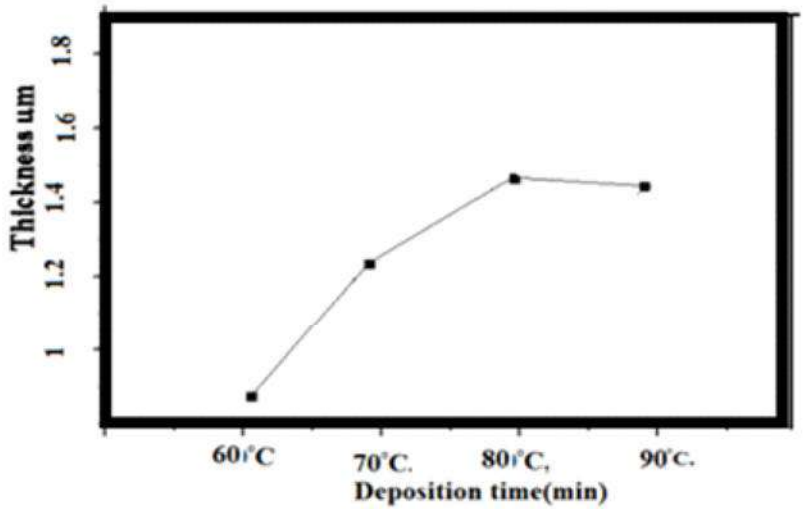

Fig 1: Thickness of ZnO thin films deposited at different bath temperature.

The thickness of the ZnO film was measured by weight difference

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method using sensitive microbalance. Thickness of ZnO films annealed at various bath temperatures was measured by the gravimetric weight difference method. The density of the deposited material is assumed to be the same as that of the bulk material (ñ = 5.675 g/cm^3 for ZnO films [17]. Fig. 4 shows the variation of ZnO film thickness as a function of the bath temperature. The thickness increase when the bath temperature increases.

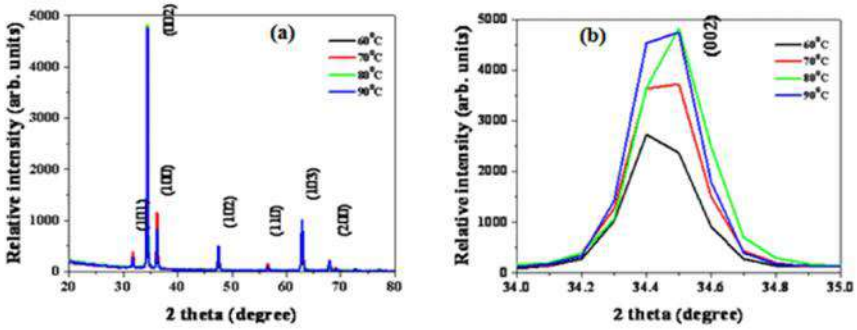

Fig 2- (a) X-ray diffractograms of ZnO thin films deposited at different bath temperature (60˚C, 70˚C, 80˚C, 90˚C).(b)Resolved (002) peak

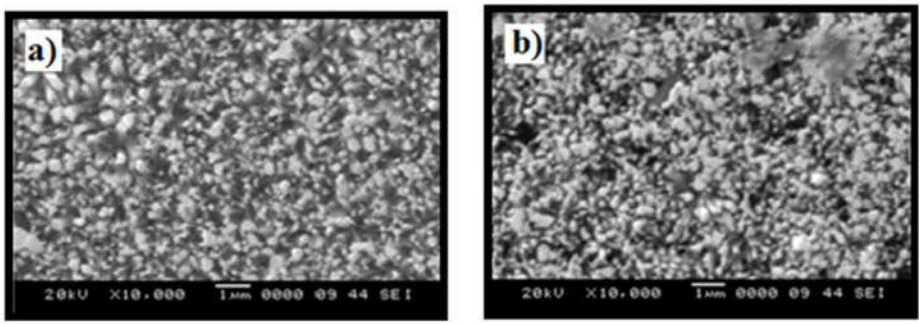

Fig 3-SEM images of ZnO samples prepared at 80˚C, and 90°C bath temperatures respectively

The XRD technique was used to confirm the nanostructures synthesized by CBD. The structure of the Films was studied using X-ray diffractomerty. Fig.2 Shows the X-ray diffractograms of ZnO thin films deposited at different bath temperature (60˚C, 70˚C, 80˚C, 90˚C). The XRD analysis revealed that the deposited Films were polycrystalline with well defined peak oriented along the (002) plane. Other orientations corresponding (100) and (101) are present with very low relative intensities as compared to that of (002) plane. This shows that grain growth, is strongly oriented along c-axis of the wurtzite structure ZnO (PDF 79-206, a = 3.2499 Å and c = 5.2065 Å), perpendicular to the substrate surface [12].The ZnO nanorods prepared at reaction temperature of 80˚C displays the strongest (002) diffraction peak, revealing that nanostructures possess well-aligned growth along the c-axis

direction. Similar results of temperature effect on the growth orientation have been reported for ZnO nanorods. [13].Fig.3 shows the surface images of ZnO samples prepared at 80°C, 90°C bath temperatures respectively. From fig 3 (a) it is seen at 80°C nanorods seems to be hexagonal with uniform orientation.

Fig (4) The optical properties of ZnO thin films prepared at various bath temperatures were investigated from variation of optical absorbance with wavelength. From fig 4 it is seen that the band gap is decreased from 3.23 -3.16 eV [14]. A blue shift in the absorption edge of ZnO could mainly be attributed to the Burstein–Moss effect, [15]

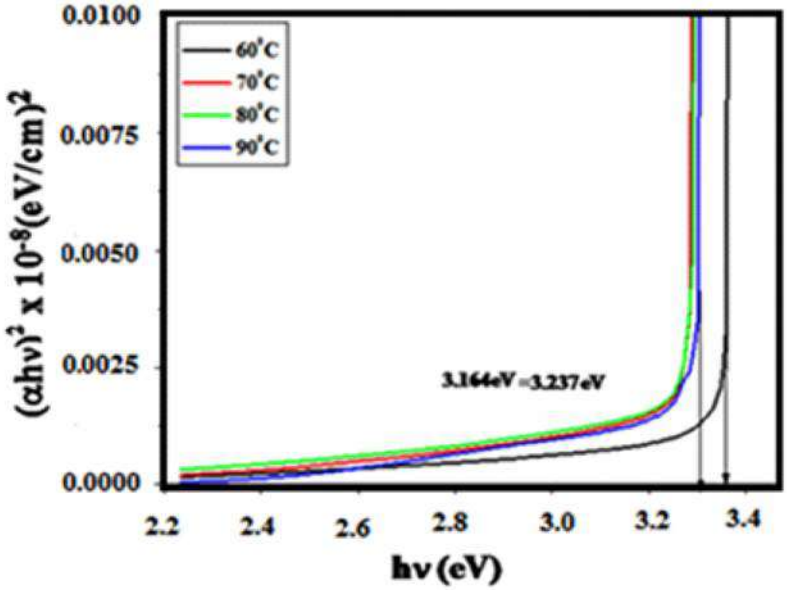

Fig 4- The band gap spectra of ZnO thin films prepared at bath temperatures 60°C, 70°C, 80°C, 90°C.

Conclusions : Zinc Oxide thin films are prepared on glass substrates by the CBD technique. There is a good agreement between XRD, SEM, and optical results. These studies show that the bath temperature contributes noticeably to the growth and to the structure of deposited films. The thickness increases as bath temperature increases. The band gap is found to be increased from 3.11 to 3.16 eV.

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Historical Perspectives of Tribes reflected in Louise Erdrich's 'Tracks'

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Introduction: The novel Tracks argue that the space between the Native and Western world's demands re-conception of home. It also suggests a type of warning to Natives who lose their connections to land, family, culture, language i.e. home. Home is not just a restoration but its power should not be transgressed, or the price of it may be too dear. Louise Erdrich's novel emphasizes the undeniable link between culture, place, heritage, people, imagination and time. Evers continues, 'By imagining who and what they are in relation to particular landscapes, cultures and individual members of cultures form a close relation with those landscapes.

The present novel relates the consequences of Fleur Pillager's selfish quest for revenge on the man named John James Mauser who stole her land. In order to enter Mauser's residence to kill him, Fleur changes her appearance as a maid in need of work. She is successful in this initial task. Her desire to make Mauser suffer all the more, ironically, ends with her accepting Mauser's an emotional request for life. She offers to take her as his new wife. Her decisions are distinct disadvantages to her, her family, and community. Fleur's temporary stay leaves her an alcoholic, daughterless, and the mother of Mauser's mixed-blood, mentally deficient son. Only in coming home does Fleur survive the ordeal, some pieces of her life never return.

In Tracks, Natives negotiate the conflicting forces of Native and Western ideologies to ensure their cultural, social, and economic survival. Tracks portray home theme in its most traditionally Native sense. The plot centres on the seemingly hopeless fight to keep Pillager and Kashpaw homelands. This struggle is worsened by in-clan fighting and the eventual split of mixed-blood families as Morrissey and Lazarus who wish to sell their lands.

John Gamber have done much to argue similar points, it is also beneficial to view Erdrich's Tracks in light of Edward Said's understanding of Poetics of Space. Said contends 'The objective space of a house its corners, corridors, cellar, rooms are far less important than what poetically it is endowed with, which is usually a quality with an imaginative or figurative value we can name and feel'. Erdrich's Tracks is the creation of the world and its people with such fidelity and power that they become part of the common memory. Place, Imagination, people,

Cryptocurrency and Bitcoin : Future Works, Opportunities and Challenges

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Introduction : First and foremost, Bitcoin was the world's first Cryptocurrency as well as its first digital money in the 21st century. They are in great demand as there is no central authority or government to oversee them, which is why they are in high demand. Because they are virtual, they cannot be taken by a law enforcement entity in the same way that cash can. Unlike fiat currencies, the transactions are safe and unaffected by manipulation, offering you piece of mind. According to others, it's going to be the next breakthrough technology, after the internet, and it's going to give birth to a worldwide currency. Cryptocurrency transfers generally require transmitting bitcoins that are priced according to market conditions. If you're accustomed with fiat money, you may think of Bitcoin as a gold standard for electronic tokens that have no underlying commodity to sustain their value. Since Bitcoins are housed in an electronic wallet or electronic address, they cannot be physically touched or carried about manner traditional money can. A bitcoin's worth is defined by its usage and applications, not its intrinsic value. The larger the demand, the bigger the supply. Since there are a limited quantity of Bitcoins in circulation, a spike in demand equates to an increase in price. There are payment system elements to a Bitcoin protocol, facilitating the transfer of money value between parties to a deal. Instead of transferring national or international currencies such as the Indian rupee or the United States dollar, the process of transfer is based on monetary worth.

Research Methodology : This research paper is studied on the basis of secondary data collected from various articles, journals, books, newspapers and internet related to bitcon and crypto currency.

Objective of the Study :

1. To study bitcoin and cryptocurrency application and challenges
2. To study improvement and future work on cryptocurrencies
3. To study legal status of bitcoin in India
4. To study advantages and disadvantages
5. To study opportunities and challenges of bitcoin in India

Bitcoin and Cryptocurrency- Applications and Challenges

As the first Cryptocurrency and the digital money of the 21st century, Bitcoin

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Representation of Inhumanity in Manjula Padmanabhan's Lights Out

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In the history of Indian English drama, there are few women dramatists, and Manjula Padmanabhan is one of them. She (born 1953) is an Indian playwright, journalist, comic strip artist, and children's book author. Even though, her writing revolves around women centric issues like gang-rape, dowry-deaths, marginalization, violence against women etc., she never calls herself as a feminist. Her play *Lights Out* (1984) delineates violence against females through the real incident of gang rape that took place in Santa Cruz in Mumbai in 1982.

India experiences brutalities against women every day. This underlines that women are not safe in this Indian patriarchal society. The experiences of inhumanity, fear, insecurity, and violence threaten women's existence on this land. The story introduces the middle class couple, Leela and Bhaskar, who lives in an affluent upper floor. One woman in the nearby under construction building is being raped day by day. Instead of taking strong action against it, and punishing the rapist, Leela's husband and even other members do not do anything to stop that unbearable crime. This so-called high profile educated society is busy only in passing opinions and making judgments. Throughout the play, Leela suffers a lot due to a traumatic experience of violence. She feels insecure and threatened, and urges for help. Unfortunately, nobody helps her. This underlines the inhumanity and hypocrisy of the society.

The present paper is an endeavour to study the play in the perspective of representation of inhumanity. The drama throws light on the paralysed society. It examines the conflict between expectations from others and evading one's own responsibilities.

Representation of Inhumanity in Manjula Padmanabhan's *Lights Out*

Light's Out is a realistic play about a disgusting subject that is a gang rape. The play artistically throws light upon the darkness in Indian society. Caste discrimination, gender discrimination, corruption are like cancers of the socio-political growth. Among them the gender discrimination has suppressed and oppressed women's freedom, happiness and rights. Domestic violence, dowry deaths, acid attacks, fire burning, sexual assaults, kidnapping, abduction, indecency, insult to modesty, rape, and many more are the various crimes against women. Among them rape is the fourth most common crime against women in India.

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A review on gas sensor - Current challenges and problems

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Introduction: In recent years, there is a great deal of interest in implementing sensing devices so as to improve environmental and safety control of toxic and inflammable gases [1]. There is also an immense need for the development of gas sensors which have numerous applications in automotive and industrial manufacturing, medical diagnostics and health care, defense and security, detection of harmful gases in mines, grading of agro-products like coffee and spices, in packaging quality control, in weather stations, etc.The solid state gas sensors work on the principle of change in physical and/or chemical properties of their sensing materials when exposed to different gas atmospheres. Taking into account that the sensing phenomena mainly take places on the material surface, the surface morphology has an essential role on the sensitivity of solid state sensor. In the last years, the nanograined materials offer new opportunities for enhancing the properties and performances of gas sensors. Several research reports have confirmed the beneficial effect of nanostructure on the sensor performance [2].

Gas sensors have a great influence in many areas such as environmental monitoring, domestic safety, public security, automotive applications, spacecraft's, houses and sensors networks. Detection is necessary in different fields such as industrial emission control, household security, vehicle emission control and environmental monitoring [5]. The semiconductor gas sensorshave got remarkable position in science and technology than other gas sensors, due to its low cost, gives fast response behavior, low response to environmental humidity, long term stability, non-expensive and low-maintenance devices using modern technologies [6]. The literature survey reports response of ferrites as sensors towards various gases. Gopal Reddy reported nickel ferrite exhibiting good response towards chlorine. Mulla and co-workers synthesized zinc ferrite which gives sensitivity towardsH_2S gas. Recently, Xiang feng synthesized nanotubes and nanorodes of nickel ferrite using a hydrothermal method that was found to be sensitive to wards triethylamine. Most of the researchers have focused on detection of LPG, SO_X, H_2S_2, H_2, NO_X and NH_3 because of their toxicity, their relation with atmospheric composition or to their high levels in some environments. Organic vapours such as methanol, acetone

Theoretical Introduction of Photocatalysis and its Application : A Review

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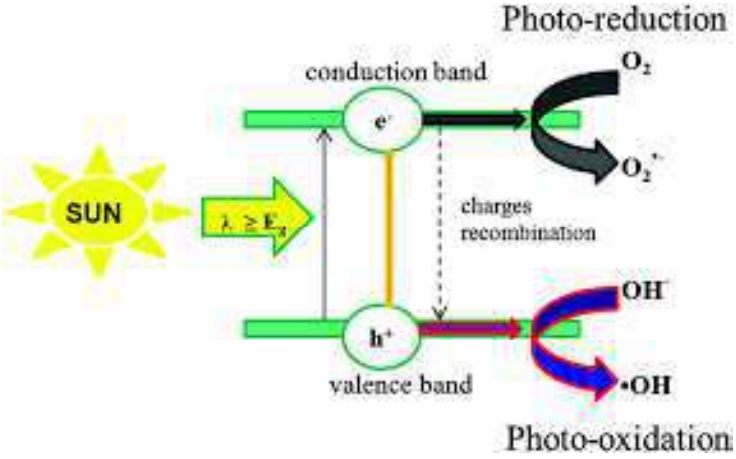
Introduction : When a light source interacts with a material's surface (i.e. semiconductor materials) the process or activity known as "photocatalysis. For this process, at least two processes must occur at the same time; an oxidation reaction using photogenerated holes and a reduction reaction using photogenerated electrons. The photocatalyst species itself should not alter in any way while the process is underway, hence the two aforementioned processes must precisely synchronize at the same time. Earle 1972, Fujishima and Honda are recognized as the pioneering scientists who successfully accomplished electrochemical photocatalysis of water at a semiconductor electrode.[1] Subsequent research revealed that TiO_2 (titanium dioxide) aids in the breakdown of cyanide in water, which in turn led to an increase in interest in the material's potential environmental uses.



Fig,1- Basic reaction mechanism of photocatalysis

The decomposition of various pollutants and improvement of atmospheric quality are both possible in a real-world setting through the effective and practical application of photocatalysis. As a result, the building and construction sector can employ the photocatalysis process to enhance indoor air quality. With the aid of doped or undoped nanostructure materials, possible photocatalytical applications

Ethnobotanical Study of Traditional Medicinal Plants Used By Tribes of Gondia District, Maharashtra, India

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Introduction : The primary goal of the current study is to gather data on the plants that the Gond and Mana, a primitive tribal population in Maharashtra's District Gondia, have traditionally used. Since ancient times, people have employed plants in traditional medicine. There are several therapeutic plants in India. Floristic wealth abounds in the nation's herbal treasure. The study of how people and plants interact to produce medicine, food, shelter, clothes, fuel, fodder, and other household needs is known as ethnobotany (Balick, 1996). It discusses the relationships that exist between the local population and the native vegetation. The goal of ethnobotanists is to investigate the various uses of these plants, including food, clothing, shelter, fodder, fuel, and furniture, as well as the connections between the medical properties of these plants and other traits of the plant species. They employ anthropological techniques to comprehend and gather information about important plants (Ram *et al.,* 2004). Central India is among the regions in India where a significant portion of the population consists of forest dwellers and tribal people (Jain*,* 2010; Mishra *et al.,* 2010).Their study uncovered a wealth of lesser-known plant applications as well as fascinating information regarding ethnomedicinal plants. Herbal medicine has long been used in various regions of Maharashtra, particularly in the Gondia District, to cure a wide range of ailments. Thus, in order to gather data that could be helpful for future research on the medicinal plants of Maharashtra's Gondia district, an ethno-medical study was conducted. There are numerous tribal communities in the state of Maharashtra that are home to people from different ethnic backgrounds. These forest inhabitants have extensive knowledge of many facets of plants and reside in forests. Gondia district is an administrative district in the state of Maharashtra, India. The district headquarter is located in Gondia. The district is part of Nagpur Division. Gondia district lies at latitudes 20.39 and 21.38 north and longitudes 79.27 to 80.42 east (Chaturvedi R. and Rokde, 2017). Gond and Mana are the major tribal communities

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ISOLATION AND IDENTIFICATION OF FUSARIUM SPS. CAUSING FUSARIUM STEM CUTTING ROT OF GERANIUM

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Abstract
Geranium is perennial aromatic herb cultivated under different agro climatic conditions in India. Fresh biomass has been used to obtain oil by steam distillation methods, oil is used in high grade perfumery Therefore, there is need to increase biomass production of Geranium. Although *Fusarium* cutting rot caused by *Fusarium* sps. It reduces the quality of oil and yield of Geranium. The present research work helps in the proper management of this disease.
Key words: - *Geranium*, *Fusarium*, Isolation

I. INTRODUCTION

Geranium (*Pelargonium* × *hortorum* Bailey) is considered one of the most popular greenhouses, potted and bedding plants worldwide. The genus Pelargonium includes annuals and herbaceous perennials, shrubs and subshrubs, and both evergreen and deciduous plants [1].
Geranium is aromatic plant and many benefits within the medical and pharmaceutical fields and chemical industries [2]. Geranium plants are liable to attack by several pathogens, causing severe losses in geranium plant production and quality [3-5]. Stem Cutting rot is one of the destructive disease of geranium caused by *Fusarium* sps. Geranium plants are susceptible to root diseases caused by various soil borne fungi, which include *Fusarium* spp. [6] and Pythium spp.[7-9] and *Rhizoctonia* spp.[3]. In the present paper deals with detection of root rot disease and isolation and identification of plant pathogens for minimizing the loss of yield.

II. MATERIALS AND METHOD

2.1 Source of diseased plants:

Geranium plants showing typical symptoms of stem cutting rot were collected from different localities from Satara and Sangli districts. (Bhilar, Medha, Panchgani andDahiwadi) during winter season in 2022.

Madhya Bharti
Humanities and Social Sciences

मध्य भारती
पत्रिकी एवं रामाजविज्ञान की त्रिभाषी शोध-पत्रिका

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SURVEY OF WILT DISEASE OF SOYBEAN IN SATARA DISTRICT

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Abstract

Wilt is the most destructive disease and causes 30% loss of soybean. An intensive survey was carried out for to assess the incidence of wilt disease during the year 2019-21 from the different localities of Satara district. The various fungal pathogens were isolated from these diseased samples of soybean. *Fusarium lateritium* was newly reported from these samples. These data will helps in understanding the risk of soybean wilt disease may aid in the development of more effective management practices.

Keywords: Soybean, *Fusarium*, *Glycine max*, Soybean

I. INTRODUCTION

Soybean (Glycine max (L) .Merr.) is one of the most valuable oil yielding crop belongs to family Fabaceae cultivated worldwide [1]. It is the rich source of oil and protein. Seed contain about 190 to 230 g/kg oil and about 380 to 420 g/kg protein on dry weight basis [2]. This economically important oil crop suffering to various diseases i.e. seeds, seedlings and roots causing Damping off, root rot and wilt, theses diseases resulting in serious yield loss. [3, 4]. Among theses diseases Wilt is most widely distributed and destructive disease caused by *Fusarium lateritium*. The present survey will helps in the management of wilt disease of soybean.

II. MATERIAL AND METHODS

The diseased samples were collected from different localities of soybean fields in Satara districts (Pusegaon, Kalambi, Dahiwadi, Koregaon, Wai and Karad) brought to research laboratory in clean sterilized polythene bags. Different fungal pathogens were isolated from these samples on Czapek dox agar medium. Sample inoculated plates were then incubated at 26 ± 2 °C for 7 days in BOD incubator. The Fungi were identified by using standard mycological literature. [5-6] and from National Fungal Culture Collection of India (NFCCI) Agharkar Research Institute, Pune.

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III. EXPERIMENT AND RESULTS

The survey of above mentioned localities of soybean field showed different fungal pathogens *Rhizoctonia solani, Fusarium lateritium, Sclerotium rolfsii Macrophmina phaseolina* and *Pythium* sps.

Table 1 shows the different localities and fungal pathogen isolated from the soybean.

Table 1. Experiment Result

Sr. no	Locality	Pathogen isolated
1	Pusegaon	*Rhizoctonia solani, Fusarium lateritium, Aspergillus niger, Pythium* sps.
2	Kalambi	*Fusarium lateritium, Sclerotium rolfsii, Aspergillus flavus, Pythium* sps.
3	Dahiwadi	*Macrophomina phaseolina, Fusarium lateritium, Rhizoctonia solani, Pythium* sps.
4	Koregaon	*Pythium* sps., *Fusarium lateritium, Sclerotium rolfsii*
5	Wai	*Rhizoctonia solani, Pythium* sps., *Macrophomina phaseolina, Fusarium lateritium.*
6	Karad	*Aspergillus niger, Pythium* sps., *Fusarium lateritium.*

IV. CONCLUSION

Among all these collected samples *Fusarium lateritium* was found most common causing wilt disease responsible for a great loss of soybean yield.

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Isolation and Identification of Fusarium SPS.Causing Fusarium Root Rot of Soybeans

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Introduction : Soybean [Glycine max (L.) Merrill] is one of the most important crops in India in terms of production, profitability and national income. Use of fungicide in seed treatment of soybean has the aim to protect the seeds and seedlings from root rot disease which can severely affect crop establishment and yield. Root rot defined as the anoxic condition in the soil around the roots of plant cause them to rot by soil borne pathogens such asFusarium spp.,Phytophthora spp.,Pythium spp.,Rhizoctonia spp. Soybean crops are amenable to attack by several pathogens, causing stringent losses in soybean crop production and quality. Root rot is one of the catastrophic disease of soybean caused by Fusariumsps.Soybean crops are vulnerable to root diseases caused by various soil borne fungi, which include Fusariumspp and Pythium spp. andPhytophthoraspp and Rhizoctonia spp. In the present paper deals with detection of root rot disease and isolation and identification of plant pathogens for curtailing the loss of yield.

Material and Methods

2.1 **Source of diseased plants :** Soybean crops parading ordinary symptoms of root rot were collected from different localities from Satara district.(Khatav, Karad,Koregaon, and Dahiwadi) during kharif or wetseason in 2022.

2.2 **Isolation, purification and identification of soybean root rot pathogens :** Soybean crops parading ordinary symptoms was collected and brought to research laboratory. Small pieces were surface-sterilized in 1 % sodium hypochlorite solution for 2 min, then washed in sterile distilled water for 4 min. Small pieces were dried between layers of sterile filter papers and were transferred to Czapek'sDox Agar medium in Petri dishes, where dishes were incubated in incubator at temperature 23±2 ÚC for 2-4 days. The obtained fungal colonies were purified using hyphal tip techniques on Czapek'sDox Agar (CDA) medium in Petri dishes where dishes were incubated in incubator at temperature 25±2 ÚC for 10-14 days. Stock cultures were maintained on CDA slants and kept in a refrigerator at 5 ÚC till use. Identification of the isolated fungi were carried out based on microscopic and culture characteristic for Fusarium spp.However, pathogenicity

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Isolation and Identification of Fusarium SPS.Causing Fusarium Root Rot of Soybeans

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Ethnobotanical Study of Traditional Medicinal Plants Used By Tribes of Gondia District, Maharashtra, India

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Introduction : The primary goal of the current study is to gather data on the plants that the Gond and Mana, a primitive tribal population in Maharashtra's District Gondia, have traditionally used. Since ancient times, people have employed plants in traditional medicine. There are several therapeutic plants in India. Floristic wealth abounds in the nation's herbal treasure. The study of how people and plants interact to produce medicine, food, shelter, clothes, fuel, fodder, and other household needs is known as ethnobotany (Balick, 1996). It discusses the relationships that exist between the local population and the native vegetation. The goal of ethnobotanists is to investigate the various uses of these plants, including food, clothing, shelter, fodder, fuel, and furniture, as well as the connections between the medical properties of these plants and other traits of the plant species. They employ anthropological techniques to comprehend and gather information about important plants (Ram *et al.,* 2004). Central India is among the regions in India where a significant portion of the population consists of forest dwellers and tribal people (Jain*,* 2010; Mishra *et al.,* 2010).Their study uncovered a wealth of lesser-known plant applications as well as fascinating information regarding ethnomedicinal plants. Herbal medicine has long been used in various regions of Maharashtra, particularly in the Gondia District, to cure a wide range of ailments. Thus, in order to gather data that could be helpful for future research on the medicinal plants of Maharashtra's Gondia district, an ethno-medical study was conducted. There are numerous tribal communities in the state of Maharashtra that are home to people from different ethnic backgrounds. These forest inhabitants have extensive knowledge of many facets of plants and reside in forests. Gondia district is an administrative district in the state of Maharashtra, India. The district headquarter is located in Gondia. The district is part of Nagpur Division. Gondia district lies at latitudes 20.39 and 21.38 north and longitudes 79.27 to 80.42 east (Chaturvedi R. and Rokde, 2017). Gond and Mana are the major tribal communities

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Nanoparticle Synthesis Methods : Bridging Innovation and Precision

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Mr. Dinesh Ashrukant Sasane (Asst. Prof.)
Dr. Patangrao Kadam Mahavidyalaya, Ramanandnagar, (Burli)

Introduction: Nanoparticles are tiny particles with dimensions in the nanometer range, typically between 1 and 100 nanometers. They can be composed of various material, including metals, semiconductors, polymers, and organic or inorganic compounds.[1] The unique properties of nanoparticles arise from their small size, which leads to a high surface area-to-volume ratio and quantum effects.[2]

Key Characteristics of Nanoparticles:

1. Size: Nanoparticles are extremely small, often on the scale of atoms and molecules, ranging from 1 to 100 nanometers.

2. Surface Area: Due to their small size, nanoparticles have a high surface area relative to their volume, which makes them highly reactive and useful for various applications.

3. Quantum Effects: At the nanoscale, materials exhibit quantum effects that differ from the properties observed in bulk materials. These effects can include changes in optical, electronic, and magnetic properties.

4. Versatility: Nanoparticles can be engineered to have specific properties by manipulating their size, shape, and composition. This versatility makes them valuable in a wide range of applications.

5. Interactions: Nanoparticles can interact with biological systems, tissues, and cells in ways that larger particles or bulk materials cannot. This property is exploited in various fields, including medicine and biotechnology.[3]

Objectives:

• Provide an overview of major nanoparticle synthesis methods.

• Explore recent advancements in nanoparticle synthesis techniques.

• Discuss the potential applications of nanoparticles synthesized through different methods.

Challenges and Concerns:

1. Toxicity: The potential health and environmental impact of nanoparticles is a concern, especially when they are used in consumer products or medical applications.

2. Regulation: Due to the unique properties of nanoparticles, regulatory frameworks may need to be adapted to address their specific challenges and ensure safety.

3. Ethical Considerations: The ethical implications of using nanoparticles

A review on gas sensor - Current challenges and problems

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Introduction: In recent years, there is a great deal of interest in implementing sensing devices so as to improve environmental and safety control of toxic and inflammable gases [1]. There is also an immense need for the development of gas sensors which have numerous applications in automotive and industrial manufacturing, medical diagnostics and health care, defense and security, detection of harmful gases in mines, grading of agro-products like coffee and spices, in packaging quality control, in weather stations, etc.The solid state gas sensors work on the principle of change in physical and/or chemical properties of their sensing materials when exposed to different gas atmospheres. Taking into account that the sensing phenomena mainly take places on the material surface, the surface morphology has an essential role on the sensitivity of solid state sensor. In the last years, the nanograined materials offer new opportunities for enhancing the properties and performances of gas sensors. Several research reports have confirmed the beneficial effect of nanostructure on the sensor performance [2].

Gas sensors have a great influence in many areas such as environmental monitoring, domestic safety, public security, automotive applications, spacecraft's, houses and sensors networks. Detection is necessary in different fields such as industrial emission control, household security, vehicle emission control and environmental monitoring [5]. The semiconductor gas sensorshave got remarkable position in science and technology than other gas sensors, due to its low cost, gives fast response behavior, low response to environmental humidity, long term stability, non-expensive and low-maintenance devices using modern technologies [6]. The literature survey reports response of ferrites as sensors towards various gases. Gopal Reddy reported nickel ferrite exhibiting good response towards chlorine. Mulla and co-workers synthesized zinc ferrite which gives sensitivity towardsH_2S gas. Recently, Xiang feng synthesized nanotubes and nanorodes of nickel ferrite using a hydrothermal method that was found to be sensitive to wards triethylamine. Most of the researchers have focused on detection of LPG, SO_X, H_2S_2, H_2, NO_X and NH_3 because of their toxicity, their relation with atmospheric composition or to their high levels in some environments. Organic vapours such as methanol, acetone

The Importance of Yoga for Healthy Life

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The main aim of yoga is integrating the body, mind, and thoughts so as to work for good ends. Modern life style leads to diseases, which are mostly due to poor food habits, heavy daily routines and to air and water pollution in turn easily affect the human body. That means growth for all parts of ourselves, not just for our bodies. We create unity between our hearts and our choices.The Three Pillars of Human Life That Yoga Nourishes i.e. Mind, Body and Spirit. Yoga means unity.Yogais essential for healthy life, for relief the stress, leave away from disease. Yoga meansPranayama, Shirshasan, Shavasan, sitting yogasane, standing yogasane.It refreshesthe mind and body.Theimportance and benefitsof yoga is for everyone in human life.Health is Wealth.

Yogais an important part in human life. In the 21st century, we face the number of stressful events in our daily life. So, there is a need to get relief from all such stressesand tension. By the help of physical exercise and yoga, we can get the energy for internal and external physical fitness. We should give some time tomaintain our body. It makes our life happy and healthy. It increases our stamina and becomes our mood fresh. Yoga had its importance in the ancient time also.

Yoga can help to address any muscular imbalances, lengthening tight areas and strengthening weak areas. Our posture can often deteriorate as we age, in a large part due to our habitual movement patterns during the day. For instance if you spend a long time working at a computer, you may find yourself vulnerable to slumping with rounded shoulders. Over time the back muscles become weak, and the chest muscles become tight, exacerbating the rounded posture. Yoga can help you to stretch out the chest and strengthen the muscles of the back. It can also make you far more aware of your body and posture, so that you find yourself automatically self-correcting to come into a healthier alignment throughout the day.

Patanjali is known as the father of modern yoga. Yoga offers physical and mental health benefits for people of all ages. And, if you are going through an illness, recovering from surgery or living with a chronic condition, yoga can become an internal part of your treatment and potentially Hasten healing. Yoga improves strength, balance and flexibility. Slow movements and deep breathing increase blood flow and warm up muscles, while holding a pause can build strength. Yoga helps with back pain relief. There are some benefits of yoga as following:

Catalytic activity of an acidic ionic liquid as a solvent for the synthesis of Coumarin derivatives

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Introduction : Coumarin are an important class of benzopyrones being the core unit of different natural products and exhibit a spectrum of biological activity'. Naturally occurring Coumarin are found in many plants, notably in high concentration in Tonka bean, woodruff, lavender, licorice, strawberries, apricots, cherries, cinnamon, sweet clover and bison grass having vanilla like flavor, Coumarin be bound their class name to 'coumarou' the vernacular name of the Tonka bean (Dipteryx odorata willd, Fabaceae), from which Coumarin itself was isolated in 1820 by Vogel[2]. Due to the potential application in fragrance, pharmaceutical and agrochemical industries it occupies an important position in natural and synthetic organic chemistry. Coumarin comprises a vast array of biologically active compounds with several types of pharmaceutical agents possessing anticancer, anti-HIV, anticoagulant, spasmolytic and antibacterial activity, and cytotoxic activity in vitro and in vivo". Natural Coumarin, such as calanolides, isolated from Calophyllum genus has shown potent anti-HIV activity. Wedelolactone 1(Figl) is another naturally occurring product that is used as a venomous snake-bite antidote; and Novobiocin 2 (Fig 1) is an antibiotic, which acts as a competitive inhibitor of the bacterial ATP binding gyrase B subunit. Many synthetic compounds, which contain the Coumarin moiety, are well known for their odor, stability to alkali, and availability. They are widely used in perfume, soaps and detergents and in the preparations of insecticides, optical brightening agents". Coumarin was once used as a food flavoring, but was banned by the FDA due to carcinogenicity. Some 3-substituted and 7-hydroxycoumarins have been shown to act as photo table laser dyes that emit in the blue-green region of the visible spectrum. The emission range increases when the 3-substituent is a heterocyclic moiety9, Coumarin also act as intermediates for the synthesis of furocoumarins, chromenes, coumarone and 2- acylresorcinols.

Because of their varied biological activities, the preparation of Coumarin and its derivatives has attracted the attention of organic chemists. Various synthetic methods have been developed for the synthesis of Coumarin. These include use of the Knoevenagel condensation, Wittig reactions, Perkin reaction and Pechmann reaction.

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(REVIEW ARTICLE)

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Watermelon as a potential nutritional horticultural crop: A comprehensive review

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Abstract

Watermelon possesses anticancer, anti-inflammatory and anti-oxidant properties due the phytochemicals like lycopene, vitamin C and polyphenolic material. Cardiovascular health conscious patients are consuming essential nutrient watermelon. Antioxidant property of watermelon plays an important role in coronary heart disease, cancer, diabetes, tension as well dehydration of body. The present review provides the information about different varieties that gain more production and keep in regulatory dietary source because of their nutritional values. It also supports to the selection of watermelon variety for more production from this ancient fruit. This information will encourage production and consumption of watermelon in worldwide.

Keywords: Anticancer; Anti-oxidant; Hypertension; Nutritional fruit

1. Introduction

In 21st century, trend of snacking has increased in recent years. However, in last few years back consumers are conscious about their health. Due to over doses of chemical fertilizers and chemical pesticides, diseases occurs like hypertension, diabetes, cancer and cardiovascular diseases (CVD) [10].

1.1. Scientific classification of watermelon:

- Kingdom: Plantae
- Clade: Angiosperms
- Order: Cucurbitales
- Family: Cucurbitaceae
- Genus: *Citrullus*
- Species: *lanatus*

1.2. Origin of Watermelon

Watermelon originated from Kalahari Desert of South Africa but now a day's watermelon cultured world widely [8,9,10]**.** Watermelon *C. lanatus* belong to the family cucurbitaceae [3]. Family cucurbitaceae is higher rank of plant families for using human food. Watermelon commonly known as Tarbooj in Hindi and Urdu, Kalingad in Marathi,

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Eipelccha in Telagu, Tormuj in Bengali, Indrack in Gujrat, Tarbuj in Manipuri and Kallangadibali in Kannada. It is an ancient fruit. It has been cultivated since 2000 BC.

1.3. Morphology of Watermelon

It is an annual plant that has a climbing in habitat having diameter about 5-6 feet. It is a large, green colour and having pinnately lobed leaves. It has a large leaves and having light yellow flowers having innocent odour. Flower followed to juicy fruit, which is special kind of berry called pepo. Fruits are variable shape and sizes usually oval or cylindrical and round. They are stripped green or plain green colour. The fleshy, juicy, edible part is red in colour with small black or brown in colour seeds [11]. A single seed plant or nursery plant consists of 2-10 flowers and flower converts into 3-5 valuable fruits and 5-8 are non economical fruits are developed it is a summer fruit having higher water content as well 55.3% juice, 31.5% rineal and 10.4% pomace.

2. Varieties of Watermelon

Watermelon has been hybridised to more yield and be more resistant against the fusarium and wilting fungal diseases. These varieties are so versatile should be grow in different climates. While, they have more resistance power and yielding capacity than ancient melon called good grainages variety. High tonnage and good production varieties available in the Indian market like Sugar queen (Syngenta), Max (BASF Nunhems), Black Boss (Indus), Big Boss (Rizwan seeds), Melody F1 (Kalash Seeds) etc.

Seeds of watermelon grow in sandy loam rich organic matter soil having good drained and pH range capacity [6]. In western India it can be sowed in October heat whereas February- March in Northern India. Optimal temperature ranges from 24-27^0 C for the growth of the vines. It can be directly seeded in field or sow in the nursery for transplantation in the field.

2.1. Worldwide Watermelon Production

Botanist referred as a pepo to watermelon. Production of watermelon in 2020, China was the topmost country for 60% of the total tonnage. Total production of watermelon was 101.6 million tonnes out for 60.1 million productions. Turkey, India, Iran, Algeria and Brazil are leading countries for production of melon.

2.2. Watermelon production in India

In India Andhra Pradesh and west Bengal are leading states for watermelon cultivation. Uttar Pradesh Andhra Pradesh and Tamilnadu are top most states for production of watermelon likewise 685.91T, 557.67T and 381.55T respectively. Maharashtra state is also leading cultivation and production of watermelon to other states.

2.3. Nutritional Values of Watermelon

The recent diet recommendation of increasing diet rich natural antioxidant has generated replacing energy dense snack per day with fruit salads as fruit juice that posses antioxidants [2,4]. It creates a huge demand in the fruit industries for nutritious fruit production from natural origin in order to consumers need. A consumer creates demand to snacks on natural products such as fruit and vegetables. Watermelon is as exotic melon fruit which contains nutrients and photochemical to be beneficial to human health [1,5]. It has good source of vitamin B, C, E as well as calcium, phosphorus, Magnesium, iron, potassium, zinc etc. [10]. Watermelon seeds consist 35%, 50% oil and 5% fibre. The natural photochemical are effective on cell growth, modulation of gene expression and immune response [4,5,9].

3. Conclusion

Watermelon is a one of the commercial and benefited horticulture crop or fruit for human health is focused in this study. This accumulated information will be encouraged more than current watermelon cultivation, production and consumption. Snacks replaced by fruits as an energy source. It is also much helpful to women at the time of menstrual phase and pregnancy. To encourage peoples by pharmacologist for more consumption of summer fruit as a functional food because of their antioxidant, antifungal, antimicrobial, gastrointestinal properties. The agronomists are to encourage the farmers for cultivation and production of watermelon to increase their economical condition.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare there is no any conflict of interest in this study.

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External Morphology of Holotrichia serrata (Fab) Adult (Coleoptera: Scarabaeidae)

S. V. Theurkar, D. N. Birhade and D. P. Gawari

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Full Length Research Article

External Morphology of *Holotrichia serrata* (Fab) Adult (Coleoptera: Scarabaeidae)

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A B S T R A C T

The national pest white grub has been defined as larvae of Melolonthidae. *Holotrichia serrata* (Fab) is a species of a Scarabaeidae family. Last five years, they cause damage to the commercial crops such as sugarcane, maize, groundnut, potato, jowar etc. and economical or medically important trees. The present investigation, external morphology of *Holotrichia serrata* was carried out in field as well as in laboratory. The *Holotrichia serrata* (Fab) adults are reddish brown in colour, compact and medium in size. The ventral side is shining; labium and labrum are fully bristly. Antenna is a lamellate type. Tibial spurs are distinguished characteristics of male and female adults.

***Key words*:** Coleoptera: Scarabaeidae, *Holotrichia serrata*, Morphology, National pest, Taxonomy

White grub is known as a 'root feeder'. Adults of white grubs are also known as 'Chaffer Beetles' or 'May- June Beetles' because of their occurrence. The white grubs have included in the category of five national pests and a large sum of money is being spent on their control at national level. The world fauna of white grub exceeds 30,000 species [1], and there are about 1300 North American species [2]. The fauna of the Indian sub-region is very rich and diverse, but it is yet to be fully explored [3]. White grub has become serious pest of most agricultural crops, vegetables, ornamental plants, fruits, pastures, turf and meadow grasses, lawns, golf courses, and forest trees in different parts of the world [4-5].

They cause heavy damage to wide variety of wild and cultivated crops [6]. In India, *Holotrichia fissa*, *Holotrichia serrata* (Fab) and *Leucopholis lepidophora* have been found so far. This infestation has been recorded throughout the country and magnitude of the problem has been widespread over the past years. The *Holotrichia serrata* (Fab) species belongs to the family Scarabaeidae. The *Holotrichia* is one of the largest Melolonthidae genuses. The larvae of most of their species feed on the roots of cultivated crops and they cause to damage the crops [7]. The grubs feed on the tap roots of the seedlings and the damaged plants wilt and die [8]. The adults feed on the leaves of host plants like *Azadirachta indica*, *Ziziphus zizyphus*, *Acacia arabica* and *Acacia catechu* [9]. White grubs have become serious pest of agricultural crops, plantation crops, pastures, fruit and meadow grasses, lawns, golf courses and forest trees in different parts of the world [4-5].

Northern Western Ghats is having various forest types such as tropical evergreen, semi-evergreen, moist and dry deciduous and high-altitude shoals mingle with natural and man-made grasslands, in addition to stream valley projects mining areas and may other land uses; and also, most of agricultural area. The *Holotrichia serrata* (Fab) is a most abundant species found in the area of Khed Tehsil which is a part of Northern Western Ghats, Maharashtra, India [10]. The *Holotrichia serrata* adult have damage the commercial growing crops as well medically important host trees. External Morphology of *Holotrichia consanguinea* Blanchard (Coleoptera: Scarabaeidae: Melolonthinae) investigated [11] but on *Holotrichia serrata* (Fab) adults have no published information regarding morphology.

MATERIALS AND METHODS

Exterior survey was carried out at different locations of Northern western Ghats for the collection of beetles. They come out from soil for feeding or mating purpose during the time 19:00 to 21:00. After feeding or mating, they go down again into the soil up to next evening. Beetles were collected handpicked and/ or shaken from the host plants *Azadirachta indica* and *Acacia arabica* during their feeding or mating period at 19:30 to 20: 45 hr. at 22± 2°C. The present study was examined in the laboratory as well in field also.

The collected beetles were identified as per the standard key [12-14], stored, pinned and dried in the laboratory and used for morphological study [15]. The microscopic examination of

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different body parts viz. mouth parts, antennae, legs, wings and genitalia.

Procedure for preparation of permanent slide

The collected beetle was dipped overnight with KOH solution to get the musculature sufficiently relaxed. After that the KOH was removed by washing in distilled water for 2-3 times. The dissection was performed within a cavity block, with the help of fine forceps and needle under the Illuminated Magnavision microscope. The dissected body parts were transferred to glacial acetic acid in another cavity block and fuschin acid was used for staining. After 10-15 minute mounted parts were again washed with glacial acetic acid to remove excess stain. Then the washed-out mounted part was transferred to Carbo- Xylol for 15 minutes. After getting clear the body parts of specimen were mounted finally on a plain slide and thick specimen on cavity slider in DPX mounting and covered with cover slip.

Drawing and microscopic photography

For photography purpose, a binocular microscope was used for microscopic structure with required magnifications and a digital camera (Sony cyber shot) was used for taking the photographs of different body parts.

For drawing purpose, a binocular microscope was used for microscopic structure with required fine magnifications and different body parts were drawn on a plain drawing paper with the Camera Lucida.

RESULTS AND DISCUSSION

The present investigation was made asses the taxonomy or morphology of *Holotrichia serrata* (Fab) adults. The adults of *Holotrichia serrata* (Fab) were dull reddish brown in colour, compact, medium in size about 20±5 mm in length and 12±4 mm width. The body is divided into three different parts; head, thorax and abdomen.

The Head is composed of sclerotized segments contain compound eyes. In male adult antennae has nine segments and female has eight segments. Scape is well developed in the socket. The male pedicle is smaller than female which is long, slender and bristly. The terminal segment of flagellum is modified into three leaves like broad plates or club shape foliate capatulum. The *Holotrichia serrata* (Fab) adult shows biting and chewing mouth parts developed for to chewing and grinding the food material. Labrum is sclerite, semi transverse and more longitudinally. It often called as upper lip. The clypeus is short, sinuate and triangular in shape. The upper lip of edges covered with bristles. The small bristles were used for testing the various types of food. The mandible or jaws are highly sclerotized paired structure. The incising and grinding region is developed for to grind the carnivorous food. The outer sides of mandible were covered by bristles. A maxilla contains basal cardo, oblong or roughly triangular stipes. The larger galea and inner lacina are well developed. The paired structure of maxilla has been covered by bristles and possesses maxillary palp. Labium is often called lower lip. It consists of three components; mentum, prementum and submentum. Mentum is usually trapezoidal and broadly joined with the submentum. Submentum is an uppermost cover of the mentum. Prementum is a sub quadrate or broadened with numerous minute bristles. On the distal margin; the prementum bears with two pair of lobes. The inner and outer pair of lobes of prementum is shown as the glossae and paraglossae respectively. The labium is a fused structure that possesses a pair of three segmented labial palps. The labial palps were covered by minute bristles. The hypopharynx is bilobed structure, oblong in shape and well-developed salivary ducts at dorsal side. Laciniae move the food upward and hypopharynx rotate the food forward and backward (Fig 1).

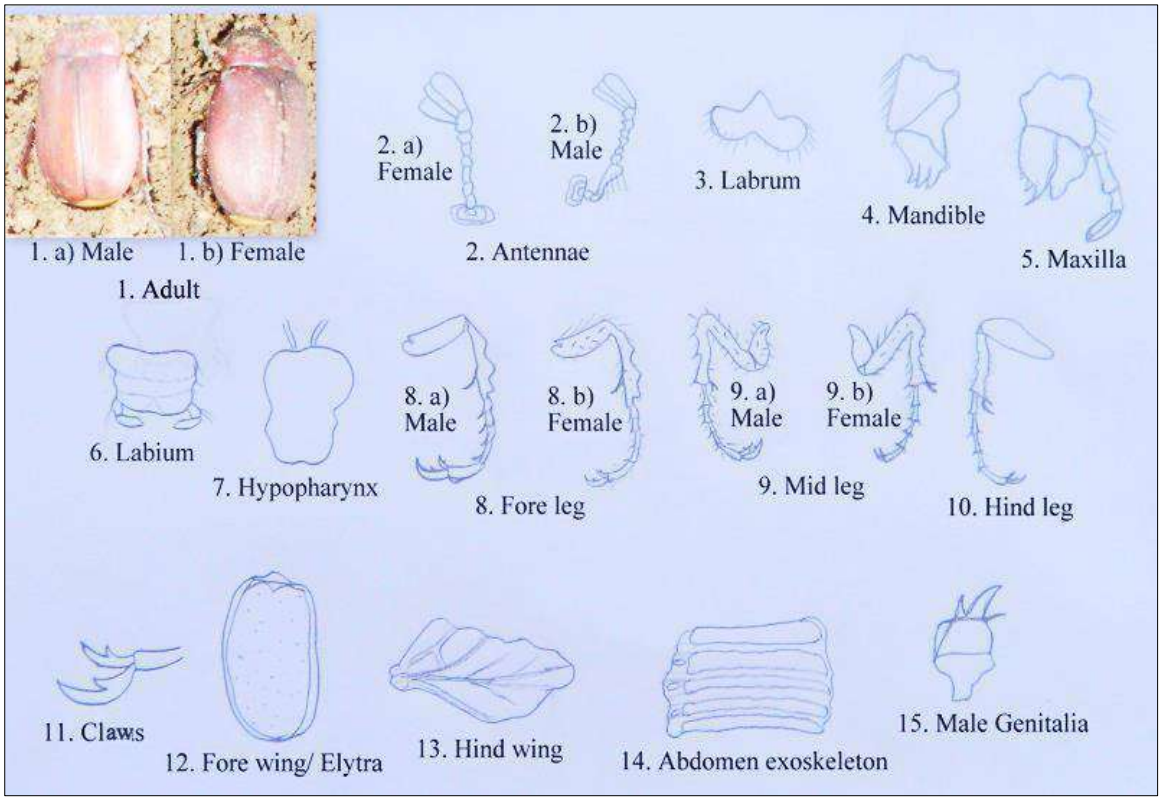

Fig 1 General external morphology of *Holotrichia serrata* (Fab) adult

The thorax is well developed. It is divided into three parts; prothorax, mesothorax and metathorax. Each thoracic segment consists pair of leg. The prothorax is well developed called as pronotum. meso and metathorax are reduced and

fused. The head is usually retracted into anterior margin of pronotum at rest and the triangular scutelum is showed between the elytra bases. Legs are well developed; adapted for walking and running. It is also supporting function for feeding and mating. The foreleg is located on prothorax. It is composed of six distinct segments; listed coxa, trochanter, femur, tibia, tarsus and metatarsus. Coxa is tubular, broad and triangular in shape. The trochanter is short, quadrangular in shape and lying in between coxa and femur. The large size femur is developed for leaping. The tibial generally long, slender, tubular and provided with the spines. It bears single spur at the middle. The pointed spur shows in male and in female adult, the tibial spur is blunt. The outer border of tibia is serrated and blunted. The tarsus is divided into five sub segments. The first five segments are equal and small in size. The distal end of tarsus is tubular and lobulated structure; bears with plantulae. The sub segmented metatarsus is long as compare to tarsus. It is developed for avoid the frictions on the smooth surface at running time. The claws are articulate with the semicircular and double pointed. Mid legs have been well developed coxa, trochanter, femur, tibia, tarsus and metatarsus. Femur is bristly. Two tibial spurs are present. Many more plantulaes are developed on tarsus at the dorsal end. The metatarsus is long as compare to the tarsus. The two claws are present at the end. Hind leg is six segmented structures. Femure is less bristly. The pointed long spurs are developed at the dorsal end of tibia. Four tarsi consist of plantulae. The double pointed claws are also present. The pairs of wings are developed only on meso and metathoracic segment. Wings are complete cover to the abdomen. Forewing is modified into elytra which are rectangular in shape, hardened, sclerotized and protect to the hind wing. Hind wing is evolved many venations developed on metathoracic segment. Hind wing is thin, transparent, partially pigmented fan like membranous structure. Blood vessels are clearly shown in the hind wing. Wings are developed for flight at the time of feeding and mating (Fig 1).

Abdomen is divided in to 5 to 7 segments. Reproductive organ developed on 5th abdominal sternum in male and 6th abdominal sternum in female. In female, sternum possesses large and small bristles are intermixed (Fig 1).

CONCLUSION

The present study concluded that the family Scarabaeidae, the *Holotrichia serrata* (Fab) adult is compact and medium in size. The male *Holotrichia serrata* (Fab) adult is smaller than female. The pronotum and scutellum in male are smaller in size than female. In male, the lamellate antennae have nine segmented; post pedicle is large or distinct and covered with bristles but in female, lamellate antennae have eight segmented, small pedicles without bristles. Upper side of labrum is totally covered by bristles. Male legs are partially covered by bristles but female legs are fully covered by bristles. Tibial spurs in male are long, pointed and sharp but in female, tibial spurs are short and blunt. The metatarsus claws are double pointed or bidif and sharp. Metatarsus is long in male than female. The *Holotrichia serrata* (Fab) adult is one of the harmful agricultural pests and it does highly need to control or manage immediately.

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Narrative of Control: Race and Hegemony in Colson Whitehead's *The Nickel Boys*

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The literary works of contemporary African American writers have been gaining international recognition for voicing an uncommon issue pertaining to racial constructs in highly ethnically diversified American society. From the arrival of the first enslaved Black people at Jamestown to the present day The Black Lives Matter Movement, the stories of black's experiences were full of inequality, injustice, violence and white hegemony. Taking this idea, the present research paper tries to study Colson Whitehead's celebrated novel The Nickel Boys in the light of race and hegemony in American society. This novel provides a terrifying tale that examines the issues of race, control and hegemony within the context of the Nickel Academy, a juvenile reform school in the 1960s Jim Crow era. This academy is a fictional reconstruction of the notorious Arthur Dozier School for Boys that ruined the lives of countless black boys by endorsing harsh beating, torture and even killing on campus.

Colson Whitehead is a significant literary figure in contemporary African American writings. He has authored seven novels and two books of non-fiction and several journalist articles on movie, book and television criticism in Weekly News and cultural paper The Village Voice. His innovative novels explore social themes related to complexities of racism with experimentation in narrative style by blending history, realism and fantasy. He is a recipient of two National Book Award as well as twice winner of Pulitzer Prize, who has been constantly shown his awareness of America's horrific racial history through his oeuvre. He received greater attention and critical acclaim in 2016 with the publication of *The Underground Railroad, a* tale of runaway teenage slave for freedom from bondage in a cotton plantation in Georgia. The release of 2019's novel *The Nickel Boys* made him the first writer to win a Pulitzer Prize for consecutive books.

The Nickel Boys is a novel set against the backdrop of the Jim Crow era and it explores the systematic mistreatment, discrimination and atrocities faced by Black teenagers within the oppressive confinement of the Nickel Academy. The novel opens with a prologue that introduces a Nickel boy Elwood Curtis, now a grownup

Elementary Education in Maharashtra

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1. Introduction : Education is one of the most important social infrastructural facilities for the development of human resources and essential for promoting the economic growth of the country. It is important in the sense that it is crucial input for empowering people with skills and knowledge and giving access to productive employment in future. Accessibility of educational facility is not only expected to enhance efficiency but also improve the overall quality of life of human being. Equitable and inclusive education is sustainable development goals for education.

The provision of universal primary education is an effective anti-poverty measures that promote equity. People are poor because they lack skill entrepreneurship. Article 45 of the constitution stipulates that the state shall endeavorto provide free and compulsory education for all children until they complete the age of 14 years within a period of ten years from the commencement of the constitution. However the task of providing basic education to all, with concrete plans of action gained greater momentum only after the national policy of education in 1986, revised in 1992 with the world declaration on education for all adopted in Jometin in 1990. Basic education, child care education, the elementary education, education to adolescents, adult education, gender equality and quality improvement have been the focus of international attention. These international developments within the country brought the need for recognizing basic education as fundamental right of every citizen on priority basis. The 86th Constitutional Amendment of 2002 led to inclusion of a new article 21-A in part III of the Indian constitution that made free and compulsory education to all children of 6 to 14 years of age. It is imperative to give good quality of elementary education to all children in the age group of 6 to 14 years. Policies and program in this direction are also necessary for achieving the goal of education under the Millennium Development Goals as well as need commitment under the National Common Minimum Programme for increasing public expenditure on education to 6 percent at the national level.

The Sarva Shiksha Abhiyan was launched toward the end of the Ninth Plan to achieve the goal of universalization of elementary education through guided by five parameters such as i) Universal Access ii) Universal Enrolment iii) Universal Retention iv) Universal Achievement and v) Equity. The aim of the programme was to provide elementary education to all children's in the 6 to 14 age group. It

RETRACTED ARTICLE: Plant nutrient dynamics: a growing appreciation for the roles of micronutrients

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This article was retracted on 07 December 2023

This article has been updated

Abstract

Micronutrients are essential for plant growth and play a key role in crop nutrition. Micronutrients such as zinc (Zn), iron (Fe), copper (Cu), and manganese (Mn) are necessary for plants and humans who rely on them directly or indirectly. These minerals are important for several important cellular functions, including respiration (Fe and Cu), photosynthesis (Fe, Cu, and Mn), and transcription (Zn). Micronutrient deficiencies have gained importance as a source of 'hidden hunger,' focusing on iron (Fe) and zinc (Zn). Enhancing the nutritional value of staple crops seems to be a simple and effective solution. We address the methods of absorption of numerous beneficial Micronutrients, their positive characteristics, and their involvement in improving crop yield. The importance of biofortification as a procedure to enhance crop yield and as an agricultural solution to solve nutritional security challenges is discussed in this review. Biofortification boosted crop yield to relieve hidden hunger and quality parameters, proving a sustainable and cost-effective strategy. Several novel and targeted biofortification strategies for nutrient enrichment of field crops, including cereals, pulses, oilseeds, and fodder crops, have been reviewed. With the information presented here, researchers can see that biofortification promises to increase agricultural production and provide the crops with additional nutrients to ensure human food security and nutrient quality.

Piper longum L.: A comprehensive review on traditional uses, phytochemistry, pharmacology, and health-promoting activities

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REVIEW

WILEY

Piper longum L.: A comprehensive review on traditional uses, phytochemistry, pharmacology, and health-promoting activities

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Abbreviations: ACE, angiotensin converting enzyme; AChE, acetylcholine esterase; ACP, acid phosphatase; AD, Alzheimer's disease; ADE, apigenin 7, 4′-dimethyl ether; ADR, adriamycin; AFM, atomic force microscopy; $AlCl_3$, aluminium chloride; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate amino transferase; AST, aspartate transaminase; BBB, blood–brain barrier; CAT, catalase; CCl_4, carbon tetrachloride; CDI, carbonyldiimidazole; CK, creatine kinase; CKMB, creatine kinase-MB; CNS, central nervous system; DGAT, diacylglycerol acyltransferase; DLA, Dalton's lymphoma ascites; DLS, dynamic light scattering; DMSO, dimethyl sulfoxide; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EAC, Ehrlich ascites carcinoma; FBG, fasting blood glucose; FRAP, ferric reducing antioxidant power; FSH, follicle-stimulating hormone; FTIR, Fourier transform infrared spectroscopy; GABA, gamma-Aminobutyric acid; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GPT, glutathione pyruvate transaminase; GR, glutathione reductase; GSH, glutathione; HA, haemagglutination assay; HDL-C, high-density lipoprotein cholesterol; HPA, hypothalamus pituitary adrenal; HUVEC, Human umbilical vein endothelial cell; IC_{50}, half-maximal inhibitory concentration; IL, interleukin; iNOS, and inducible nitric oxide synthase; LD_{50}, median lethal dose; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; LPO, lipid peroxidation; LPS, lipopolysaccharide; MAO, monoamine oxidase; MDA, malondialdehyde; MES, maximal electroshock seizures; MIC, minimum inhibitory concentration; MMI, macrophage migration index; MMP, mitochondrial membrane potential; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSG, monosodium glutamate; MSH, melanocyte-stimulating hormone; MTT assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay; NO, nitric oxide; NOS, nitric oxide synthase; NSAID, nonsteroidal antiinflammatory drugs; PAF, platelet-activating factor; PARP, procaspase-3/poly(ADP)ribose polymerase; PD, Parkinson's disease; PFC, plaque-forming cell; PI, phagocytic index; PMBC, peripheral blood mononuclear cells; PTZ, pentylenetetrazole; RBC, red blood cell; RNS, reactive nitrogen species; ROS, reactive oxygen species; SAED, selected area electron diffraction; SE, supercritical fluid extract; SEM, scanning electron microscopy; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SOD, superoxide dismutase; TC, total cholesterol; TEM, transmission electron microscopy; TG, total triglyceride; TGA, thermogravimetric analysis; TH, tyrosine hydroxylase; TIMP, tissue inhibitor of metalloprotease; TLC, thin layer chromatography; TMRM, tetramethylrhodamine methyl ester; TNF, tumour necrosis factor; TRP, total reducing power; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling; UPLC-MS/MS, ultra performance liquid chromatography-tandem mass spectroscopy; VEGF, vascular endothelial growth factor; VLDL, very low-density lipoprotein; WBC, white blood cell; α-MSH, α-melanocyte-stimulating hormone.

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Abstract

Piper longum (family Piperaceae), commonly known as "long-pepper" or "Pippali" grows as a perennial shrub or as an herbaceous vine. It is native to the Indo-Malaya region and widely distributed in the tropical and subtropical world including the Indian subcontinent, Sri Lanka, Middle-East, and America. The fruits are mostly used as culinary spice and preservatives and are also a potent remedy in various traditional medicinal systems against bronchitis, cough, cold, snakebite, and scorpion-sting and are also used as a contraceptive. Various bioactive-phytochemicals including alkaloids, flavonoids, esters, and steroids were identified from the plant extracts and essential oils from the roots and fruits were reported as antimicrobial, antiparasitic, anthelminthic, mosquito-larvicidal, antiinflammatory, analgesic, antioxidant, anticancer, neuro-pharmacological, antihyperglycaemic, hepato-protective, antihyperlipidaemic, antiangiogenic, immunomodulatory, antiarthritic, antiulcer, antiasthmatic, cardioprotective, and anti-snake-venom agents. Many of its pharmacological properties were attributed to its antioxidative and antiinflammatory effects and its ability to modulate a number of signalling pathways and enzymes. This review comprehensively encompasses information on habit, distribution, ethnobotany, phytochemistry, and pharmacology of *P. longum* in relation to its medicinal importance and health benefits to validate the traditional claims supported by specific scientific experiments. In addition, it also discusses the safety and toxicity studies, application of green synthesis and nanotechnology as well as clinical trials performed with the plant also elucidating research gaps and future perspectives of its multifaceted uses.

KEYWORDS
ethnobotany, pharmacological activity, phytochemistry, *Piper longum*, piperine, piperlongumine

1 | INTRODUCTION

Plant-based medicines have long been used to treat numerous human diseases worldwide from time immemorial. In developing countries, mainly in rural areas, herbal medicines are still the primary source of treatment. Plants are thought to play a major role in the discovery of new therapeutic agents since they are the potent reservoirs for a plethora of biologically active phytochemicals for the cure of several medical conditions (Gutierrez & Maria Neira Gonzalez, 2013). The genus *Piper* has about 2,000 species with high commercial, economical, and medicinal importance. These are widely distributed in tropical and subtropical areas of the world (Parmar et al., 1997). *Piper longum* L. (Piperaceae), generally known as long pepper or pippali is a climbing shrub or a herbaceous evergreen vine native to the warmer parts of India, eastwards to Bengal, Assam, and the Khasia mountains; westwards to Mumbai and southwards to Kerala (Bisht, 1963). *Piper longum* is a close relative to *Piper nigrum*; both contain the alkaloid piperine, which is responsible for pungency and hot flavour. *Piper retrofractum*, also known as long pepper, is native to Java and Indonesia.

Piper longum is one of the most important species in this family (Scott, Jensen, Philogène, & Arnason, 2008). Its uses are mentioned in the Indian Ayurvedic system of medicine. Traditionally the fruits, roots, and stems of *P. longum* are prepared as paste, juice, or decoction for the treatment of bronchitis, asthma, cough, and cold, as an antidote to snakebite and scorpion sting, and as a contraceptive by different aboriginals and communities (Sivarajan & Balachandran, 1994). The available literature has recommended unripe fruit of *P. longum* for respiratory disorders, gastrointestinal disorder, disorders of metabolic imbalance, as an aphrodisiac, emmenagogue, circulatory stimulant, and analgesic (Evans, 2009). *Piper longum* is one of the main ingredients in the famous formulation, "Trikatu" which is known to be a prominent bio-enhancer (Johri & Zutshi, 1992). *Piper longum* is used in Rasayana which is an important therapy in Ayurveda, dealing with the promotion of strength and vitality which is also mentioned in "Charaka Samhita" for improvement of cognitive impairment (Sharma & Samhita, 1983).

A plethora of pharmacologically active constituents was isolated from *P. longum* including major alkaloids such as piperine and piperlongumine, volatile oils containing β-caryophyllene, pentadecane, and bisabolene, along with some esters, flavonoids, lignans, terpenes, organic acids, steroids, and so on (Kumar, Marković, Emerald, & Dey, 2015). Considering the various traditional use of *P. longum*,

researchers isolated many bioactive compounds from the plant which were scientifically validated using bioactivity-guided isolation and various pharmacological experiments. A number of studies have revealed the anticancer properties of *P. longum* extract mediated by antioxidant and inflammatory mediator cytokines. The roots and fruits demonstrated weak opioid but potent nonsteroidal antiinflammatory drug (NSAID) type of analgesic activity, in addition to cardioprotective, antiarthritic, anticonvulsant, immunomodulatory, and antiinflammatory activities (Kumar et al., 2015). Plant extracts and isolated compounds were found to have inhibitory effects on bacteria, fungi, parasites, helminths, and so on. The present review encompasses comprehensive information on the habit, distribution, phytochemistry, ethnobotany, and pharmacological activity of *P. longum* as a curative agent against human ailments with a note on its safety and toxicity attributes. According to Cronquist (1988), the taxonomical classification of *P. longum* has been proposed as follows (Lawrence, 2017).

Kingdom: Plantae.
Division: Magnoliophyta.
Class: Magnoliopsida.
Order: Piperales.
Family: Piperaceae.
Genus: Piper.
Species: *Piper longum*.

2 | METHODOLOGY

2.1 | Search engines

A literature survey using the popular scientific search engines namely, PubMed, ScienceDirect, Google Scholar, Cabdirect, NOPR, and Scielo was performed thoroughly to retrieve literature using search strings such as *P. longum* with distribution, ethnobotany, phytochemistry, pharmacology, nanotechnology, clinical studies, and toxicology. Further, cross-referencing among the retrieved literature has produced a total number of 367 articles (from 1830 to 2021) (Google Scholar: 354; PubMed: 94; ScienceDirect: 43; NOPR: 9; Cabdirect: 4, and Scielo: 1). Following screening and removal of duplicates, a total number of 250 articles were selected and cited in this present review.

2.2 | Inclusion criteria

Only papers and book chapters on *P. longum* describing its distribution, traditional use, phytochemistry, pharmacology, nanotechnology, clinical studies, and safety and toxicology published in English were chosen. Other articles, conference proceedings, case reports, editorial, letters, theses, or publications that did not meet the inclusion criteria were not included in this systematic review. The selected publications were strictly verified in accordance with the inclusion criteria depicted above.

2.3 | Data extraction

All shortlisted publications were studied for publication year, country of origin, plant parts used, identifies/isolated phytochemicals, and relevant pharmacological attributes. For the bioactivity analyses, the retrieved data also represented extract/fraction used, experimental model (cellular and animal), dose, results, and ethnopharmacological relevance (if any). The verified data are presented in tables and figures and are also discussed in the present article. The process of retrieval and screening of publications for this review is presented in Figure 1.

3 | DISTRIBUTION, CULTIVATION, TAXONOMY, AND MORPHOLOGICAL DESCRIPTION

3.1 | Geographical distribution

Piper longum is native to the Indo-Malaya region. It generally grows in the warmer parts of India, from the central Himalayas to Assam, Mikir and Khasi hills, lower planes of West Bengal and evergreen forests of

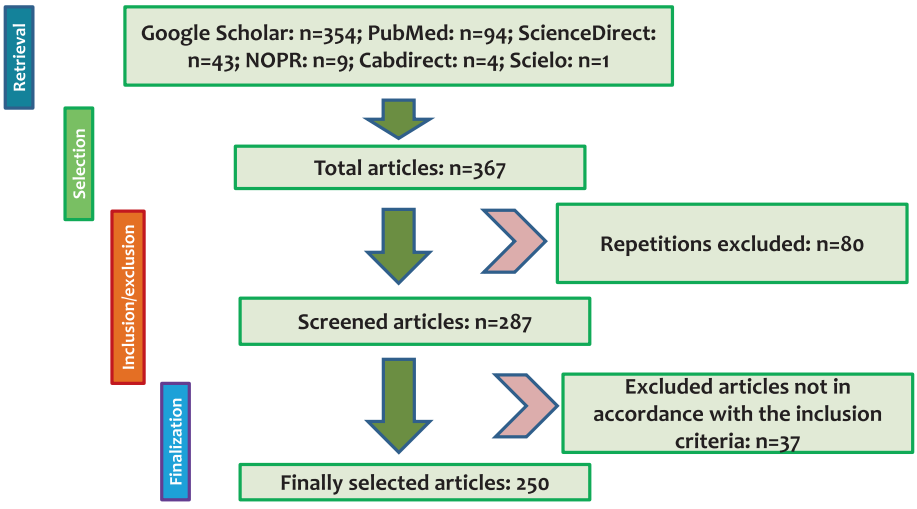

FIGURE 1 Flow diagram of selection and screening of the retrived articles

Kerala, Western Ghats from Konkan to Travancore regions, Uttar Pradesh, and is also recorded from Car Nicobar Islands. Long pepper is also found to grow wild in the tropical evergreen rainforests of India, Nepal, Indonesia, Malaysia, Singapore, Sri Lanka, Timor, and Philippines. Besides the Indian subcontinent, it is also recorded in Sri Lanka, Middle-East, and America (Sivarajan & Balachandran, 1994; www.indianspices.com/spice-catalog/pepper-long.html). Figure 2 depi cts the worldwide distribution of *P. longum*. (The exact percentage or the related data of distribution in Figure 2 is available at https://www.gbif.org/occurrence/search?taxon_key=3086338).

3.2 | Cultivation and propagation

In India, *P. longum* is mostly derived from the wild mostly collected from the states of West Bengal, Uttar Pradesh, Assam, certain parts of Andhra Pradesh, and the low hills of Annamalai and Assam (Manoj, Soniya, Banerjee, & Ravichandran, 2004). Plants are mostly grown in tropical moist and humid climates preferably in shady conditions, well-drained sandy humus soil with a pH range of 5.5–8.5, 50% shade, and laterite soil with organic matter content and good water holding capacity. They grow better in the shade of trees and as an intercrop in the coconut plantation in the plains at an altitude of 900–1,500 m (Manoj et al., 2004; Oommen, Ved, & Krishnan, 2000).

Piper longum can be propagated at the beginning of rain through vegetative means using mature branches or suckers which grow like a bushy runner. It can be grown by cutting the semi-hard stem which is planted in a nursery bed in shady condition. The tiller growing at the base of the plant can be separately planted. Plants can be developed from the root, shoot tips, leaves, and stems by micropropagation technique (Manoj et al., 2004).

3.3 | Morphological description

Piper longum is a dioecious, aromatic, evergreen, and climbing plant up to 0.9 m high with jointed stems, generally rooting at the nodes to attach to the hosts. Roots are generally woody; stems are slender, swollen at nodes, and downy; leaves are alternate, membranous, ovate to cordate, apex acute to acuminate, base oblique, glabrous, and 3–7 cm long. Flowers usually grow in solitary spikes. With the spikes, male and female plants can be distinguished as the plants are morphologically similar. The male spikes are greenish-yellow, fleshy, cylindrical (2–7.5 cm long), with orbicular bracts and 2 stamens; female spikes are shorter than male spikes (1.25–2 cm long) with circular bracts and 3 stigmas. Fruits are berries (2–3 cm long), thick, oblong, blackish-green in colour, and pungent taste; when broken show a central axis with five to six fruitlets around the axis (Evans, 2009; Wiart, 2012). Figure 3 represents the hand-drawn sketches of *P. longum*: plant morphology (a), inflorescence (b), mature fruit (c), T.S. of fruit (d), and seed €. Figure 4 presents the photographs of *P. longum*: plant habit (a), leaves (b), inflorescence (c), mature fruit (d), and dry fruits (e).

4 | TRADITIONAL USES

Long pepper (Peepal, Pipal, or Pipli) has been cited as an excellent ingredient in the Ayurveda since the times of the Vedas (Atharva

FIGURE 2 Worldwide distribution of *Piper longum* (https://www.gbif.org/species/3086338). Distribution ratio and Location information: https://www.gbif.org/species/3086338/metrics

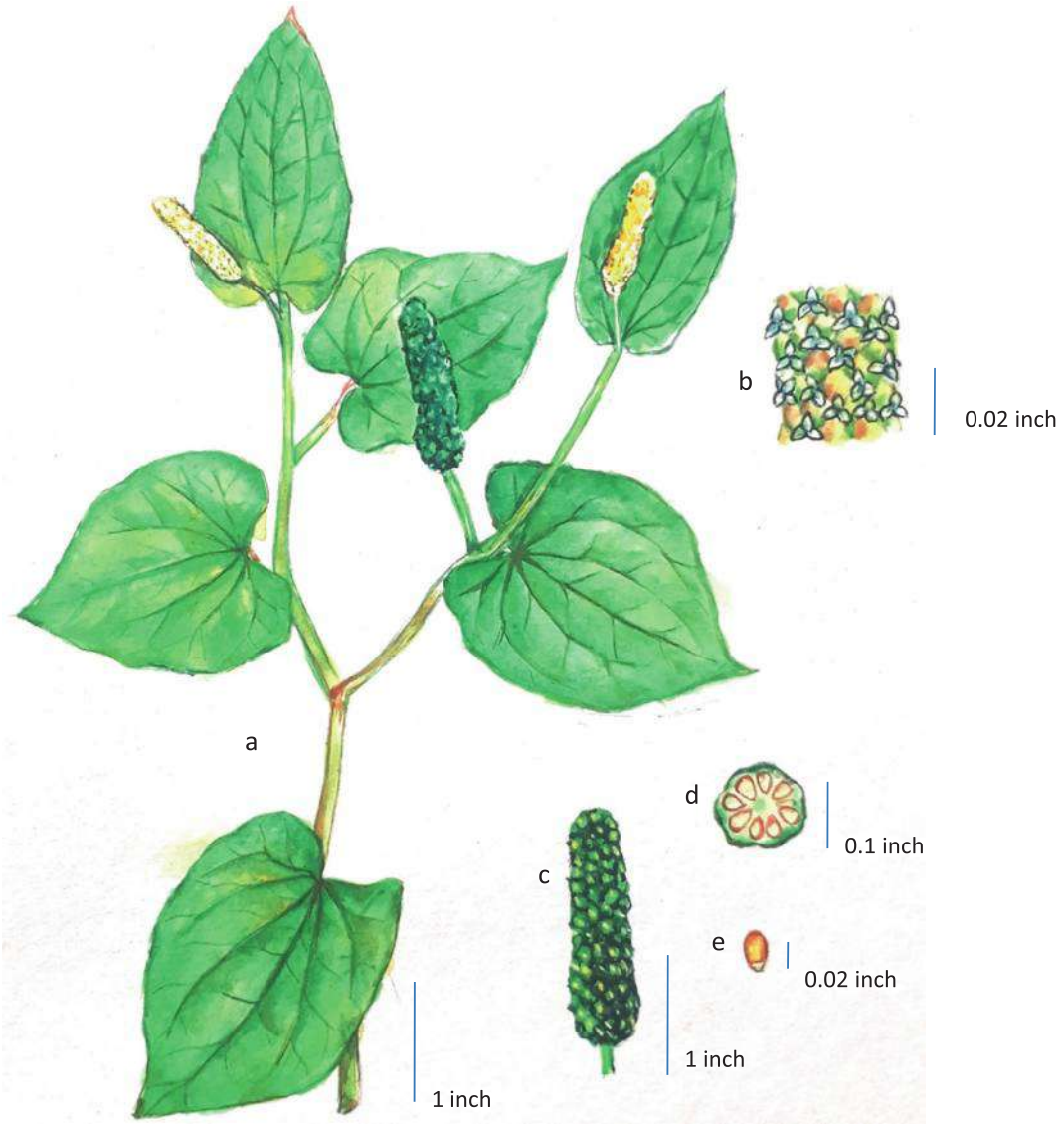

FIGURE 3 *Piper longum* plant morphology (a), inflorescence (b), mature fruit (c), T.S. of fruit (d), and seed (e)

Veda), one of the antiquarian archives of human knowledge. This plant was mentioned also in Susruta Samhita documented in the first Century A.D. by the well-known Hindu physician, Charaka, in Shri Bhav Prakasha (A. D. 1310), and Shankar Nighantu during the 14th Century (Atal & Ojha, 1965). In Europe, the species was known to the Greeks and Romans and was recorded in the book "Macer Floridus" (10th Century A. D.) as "macropiper." Later, the species got its official recognition in many pharmacopeias (Mukerji, 1953; United States of Pharmacopeal convention, 1830).

The traditional uses of *P. longum* were mostly reported from the Indo-Malay regions. A total of 135 Ayurvedic formulations of *P. longum* have been reported by Kamboj (Kamboj, 2000). Ayurvedic formulations such as Amrtariasta, Ayaskrti, Cyavanaprasa Avaleha, Gudapippali, Asvagandhadyarista, Kumaryasava, Candanasava, Siva Gutika, and Kaisora Guggulu; root formulations such as Pancakola Curna, Dasamula Taila, Dasam ulapancakoladi, Kvatha Curna, and Dasam ulastapalaka Ghrita were mentioned in the Ayurvedic Pharmacopoeia of India (The Ayurvedic Pharmacopoeia of India Parts II and IV, Ministry of Health and Family Welfare, Dept of AYUSH). In the Ayurvedic system of medicine, the fruits have been reported for their cooling effect and for being useful in biliousness which were also reported as stomachic, aphrodisiac, laxative, antidiarrhoeic, antidysenteric, and antiasthmatic, as well as against bronchitis, abdominal complaints, fevers, leucoderma, urinary discharges, tumours, piles, diseases of the spleen, pains, inflammation, leprosy, insomnia, jaundice, hiccoughs, tubercular glands, and so on (Khushbu, Roshni, Anar, Carol, & Mayuree, 2011). Avipattikara, Hingavastaka, Sitopaladi, Sringyadi, Talisadya, and Trikatu are very popular Ayurvedic (churna) medicines in India containing *P. longum* and other *Piper* species (Hazra, Chakraborty, Mitra, & Sur, 2019). In the Unani System of medicine, the roots and fruits have been used in palsy, gout, and lumbago. Besides, these have been reported as carminative, liver tonic, stomachic, abortifacient, aphrodisiac, haematinic, diuretic, digestive, emmenagogue, and so on, as well as against liver inflammation, joint

FIGURE 4 *Piper longum* (a) plant habit, (b) leaves, (c) inflorescence, (d) mature fruit, and (e) dry fruits (a and e were obtained from Wikimedia Commons and are licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license; Figures (b), (c), and (d) unpublished photo taken by PB)

pains, snakebite, scorpion-sting, and night-blindness (Khushbu et al., 2011).

Reports of uses of *P. longum* are also found in Traditional Chinese Medicinal (TCM) system for the treatment of stomach disease, and analgesia and also as a vasorelaxant. *Piper longum* has been cited as a popular medicinal herb in Yunnan, China showing many biological effects (Wang et al., 2021). *Piper longum*, has been used for a long in TCM as an analgesic and against coronary heart disease, stroke, stomach disease, and many other medical conditions (Bi et al., 2015; Hua et al., 2019; Liu, Song, & Hu, 2007). Piperine, the most abundant alkaloid of *P. longum*, was officially marked as a labelling compound by the Chinese Pharmaceutical Committee for application in the quality control of *P. longum* (Li et al., 2020; Xu et al., 2019).

The use of root in the treatment of heart diseases is recorded in ancient East Asian literature (Khushbu et al., 2011). In Europe, *P. longum* was first documented by Hippocrates as a medicament. It came to Greece in the sixth or fifth century BC, and became a popular spice prior to the European discovery of the New World (Kumar, Kamboj, & Sharma, 2011). Many herbal formulations prepared with *P. longum* are also found in countries of European Union, United States, China, and Middle Eastern countries (Singh, Ahamad, & Quraishi, 2016; Yeotkar, Nimbhorkar, Deshmukh, & Patil, 2010). Medicinal use of *P. longum* is also depicted in Islamic regions of North and East Africa (Manoj et al., 2004). However, in most cases, *P. longum* has been reported as one of the major ingredients used in different doses in many polyherbal traditional formulations.

Traditional uses of the species are mentioned in Table 1 with the using community, place of use, modes of preparations, and treated ailments.

5 | PHYTOCHEMISTRY

P. longum contains a number of secondary metabolites of various classes, such as alkaloids, lignans, flavonoids, amides, esters, essential oils, and organic acids. Alkaloids are abundant phytochemicals in all major plant parts namely fruits, seeds, leaves, stems, and roots. Piperine was the first amide isolated from the *Piper* species that also contributes to *P. longum*'s hot and pungent flavour (Lee, Shin, & Woo, 1984; Saraf & Saraf, 2014).

5.1 | Phytochemicals identified from the whole plant

The most abundant phytochemical of the *P. longum* plant is alkaloids. Liu et al. prepared an ethanol extract of *P. longum* from the whole plant and followed it up by extracting consecutively with petroleum

TABLE 1 Traditional uses of *P. longum*

Disease category	Disease sub-categories	Used by/in	Part(s) used	Preparation (s)	References
Respiratory disorders	Cough	Tharu community of Parroha VDC, Rupandehi district, Nepal	Fruits	—	Acharya and Acharya (2009)
		Upper Seti Hydropower Project, Western Nepal		Chewed	Uprety, Poudel, Asselin, and Boon (2011)
	Cough and cold	Tons river area, Dehradun	Fruits, roots	—	Kumar and Pandey (2015)
	Bronchitis	Kani tribes of Pechiparai Hills, Western Ghats, India	Fruits	Powder taken orally	Sukumaran, Sujin, Geetha, and Jeeva (2021)
	Cold, cough, emetics	Eastern Ghat of Northern Andhra Pradesh, India	Stem, roots	—	Venkaiah, Rao, and Prameela (2020)
	Respiratory tract diseases, bronchitis	Thailand, Ayurvedic and Unani systems	Roots	Root infusion taken orally	Chaveerach, Mokkamul, Sudmoon, and Tanee (2006)
	Chronic bronchitis	Kantapada block, Cuttack, Orisha, India	Fruits, roots	Roasted and mixed with honey, decoction	Sahoo and Mahalik (2020)
	Respiratory infections, cough	West and South district of Tripura, India	Roots, fruits	Fruit powder mixed with honey and root juice taken orally	Sen, Chakraborty, De, and Devanna (2011)
	Asthma	Andhra Pradesh, India	Immature fruits, roots	Powder mixed with honey or root decoction taken orally	Savithramma, Sulochana, and Rao (2007)
	Asthma, cold, and cough	Rava, Ekka, and Oraon communities of Chilapatta Reserved Forest, Cooch Behar, West Bengal	Seeds	Boiled with sugar, salt with cow milk and consumed	Shukla and Chakravarty (2012)
	Cold, cough, tonsillitis	Limbu, Bahun, Rai, Tamang tribe of Churiya, East Nepal	—	—	Oli, Ghimire, and Bhuju (2005)
	Expectorant, cough, cold, bronchitis	Durgamkonda of Veligonda Hill Range, Eastern Ghats, Andhra Pradesh, India	Leaves, fruits	—	Reddy, Paul, and Basha (2016)
	Throat infection	Chhindwara district, India	Roots	—	Dhurwe and Diwan (2019)
	Cough, sour throat, gland infection	Kanies in Mothiramalai, Kilamalai Reserve Forest, Kalial Range, Kanyakumari Forest Division, Tamilnadu	Seeds	Mixed with pepper powder, boiled, and drunk	Pradeesh, Sukumaran, and Jenisha (2020)
	Asthma, cough	Gampaha District, Western Province, Sri Lanka	Fruit	Infusion, decoction	Napagoda, Sundarapperuma, Fonseka, Amarasiri, and Gunaratna (2018)
	Asthma, bronchitis, expectorants	Rawalkot, Pakistan	Fruits	Powder, decoction	Jan, Mukhtiar, and Hazrat (2018)
	Cough, cold, bronchitis, asthma	Darjeeling region, Eastern Himalaya	Dry fruits	Taken orally	Moktan and Rai (2019)
	Lung disease	Warangal district of Andhra Pradesh, India	—	—	Vijayagiri and Mamidala (2012)
Febrifuge		Gampaha District, Western Province, Sri Lanka	Fruit	Infusion, decoction	Napagoda et al. (2018)
		Kolli Hills, Tamil Nadu	Seeds	Decoction mixed with fresh water	Kadirvelmurugan, Raju, Arumugam, Karthik, and Ravikumar (2014)
		Durgamkonda of Veligonda Hill Range, Eastern Ghats, Andhra Pradesh, India	Leaves, fruits	—	Reddy et al. (2016)

(Continues)

TABLE 1 (Continued)

Disease category	Disease sub-categories	Used by/in	Part(s) used	Preparation (s)	References
Analgesic		Durgamkonda of Veligonda Hill Range, Eastern Ghats, Andhra Pradesh, India	Leaves, fruits	–	Reddy et al. (2016)
		Lushai tribes in North Cachar Hill District, Assam	Fruits	Crushed and mixed with jaggery and ginger powder and boiled with water, taken with tea	Sajem and Gosai (2010)
Parasitic diseases	Malaria	Baksa, Assam	Leaves	Infusion taken orally	Gohain et al. (2015)
		Jonai tribal community, Assam, India	Fruits, roots	Powder boiled in water and taken orally	Wangpan, Chetry, Tsering, Tapi, and Tangjang (2016)
		Haridwar district, India		Crushed and mixed with jaggery and ginger powder	Arora (2009)
		Orissa	Fruits	Decoction taken orally	Nagendrappa, Naik, and Payyappallimana (2013)
		Lushai tribes in North Cachar Hill District, Assam		Crushed and mixed with jaggery and ginger powder and boiled with water, taken with tea	Sajem and Gosai (2010)
Digestive disorders	Indigestion	Tharu community of Parroha VDC, Rupandehi district, Nepal		–	Acharya and Acharya (2009)
		East Godavari District, Andhra Pradesh, India		–	Mortha and Lagudu (2020)
	Stomach-ache, spleen diseases, improves appetite	Thailand, Ayurvedic and Unani systems	Roots	Root infusion taken orally	Chaveerach et al. (2006)
	Stomach ache	Warangal district of Andhra Pradesh, India	–	–	Vijayagiri and Mamidala (2012)
	Carminative, lever disorders, indigestion	Durgamkonda of Veligonda Hill Range, Eastern Ghats, Andhra Pradesh, India	Leaves, fruits	–	Reddy et al. (2016)
	Promote digestion	Southern Xinjiang, China	Fruits	Herbal tea preparation	Abdusalam et al. (2020)
	To treat enlarged spleen	Jaintia tribal community of Meghalaya, India		Power mixed with honey and taken orally	Jaiswal (2010)
	Abdominal pain	Coastal districts of Odisha		In water taken after meal	Sahu, Pattnaik, Sahoo, Lenka, and Dhal (2011)
	Carminative, food digestion, tonic	Markets of Mashhad, Iran		–	Amiri and Joharchi (2013)
Rheumatism		Rava, Ekka, and Oraon communities of Chilapatta Reserved Forest, Cooch Behar, West Bengal	Seeds	Boiled with sugar, salt with cow milk and consumed	Shukla and Chakravarty (2012)
		Kantapada block, Cuttack, Orisha, India	Fruits, roots	Roasted and mixed with honey, decoction	Sahoo and Mahalik (2020)
		East Godavari District, Andhra Pradesh, India	Fruits	–	Mortha and Lagudu (2020)
		Siddha medical practitioners from Radhapuram taluk of Tirunelveli District, Tamil Nadu, India	–	–	Chellappandian, Mutheeswaran, Pandikumar, Duraipandiyan, and Ignacimuthu (2012)
Others	Antilithic (removal of stones)	Bhopal, India	Fruits, seeds	Taken in combination with different herbs	Agarwal and Varma (2015)
	Tumours	Thailand, Ayurvedic and Unani systems	Roots	Root infusion taken orally	Chaveerach et al. (2006)
	Induce the expulsion of the placenta after parturition	Thailand, Ayurvedic and Unani systems		Root infusion taken orally	
	Pregnancy disorders	West and South district of Tripura, India	Roots, fruits	Fruit power mixed with honey and root juice taken orally	Sen et al. (2011)

TABLE 1 (Continued)

Disease category	Disease sub-categories	Used by/in	Part(s) used	Preparation (s)	References
	Promote lactation, galactagogue	Sacred groves of East Godavari District, Andhra Pradesh, India	Roots, pods	Power taken orally with milk	Rampilla, Khasim, and Thammasiri (2020)
	Hypertension	Rajshahi district, Bangladesh	Leaves	Plant mixed with water taken orally	Nawaz et al. (2009)
	Culicidae, Muscidae, Dictyoptera insect repellent	Assam	Fruits, roots	Decoction of fruits and roots is taken orally	Namsa, Mandal, and Tangjang (2011)
	Religious medicine	Memba tribe of Dehang-Debang biosphere reserve, Arunachal Pradesh, India	Flowers	—	Rethy, Singh, Kagyung, and Gajurel (2010)
	Diabetes	Durgamkonda of Veligonda Hill Range, Eastern Ghats, Andhra Pradesh, India	Leaves, fruits	—	Reddy et al. (2016)
		Khudra, Odisha, India	Fruits	Paste	Mishra, Mahalik, and Parida (2019)
		Bodo tribe of Kokrajhar district, Assam		Raw	Daimari, Roy, Swargiary, Baruah, and Basumatary (2019)
	Inflammation	Durgamkonda of Veligonda Hill Range, Eastern Ghats, Andhra Pradesh, India	Leaves, fruits	—	Reddy et al. (2016)
	Insomnia	Durgamkonda of Veligonda Hill Range, Eastern Ghats, Andhra Pradesh, India		—	Reddy et al. (2016)
	Health promoting	Mishing tribe, Assam	Dry inflorescence	Poro apang preparation	Pawe and Gogoi (2013)
	Tonic, stimulant	Durgamkonda of Veligonda Hill Range, Eastern Ghats, Andhra Pradesh, India	Leaves, fruits	—	Reddy et al. (2016)
	Tonic, promote digestion	Southern Xinjiang, China	Fruits	Herbal tea preparation	Abdusalam et al. (2020)
	To enhance power	East Godavari District, Andhra Pradesh, India		—	Mortha and Lagudu (2020)
		East Godavari District, Andhra Pradesh, India		—	
	Aphrodisiac	Turkey		Paste	Güven (2011)
	Urinary problem	Mishing tribe, Assam	Dry inflorescence	Poro apang preparation	Pawe and Gogoi (2013)
	Snake bite	Tribal people of Koraput district of Odisha, India	Leaves	Paste given orally	Kumar, Padhan, Palita, and Panda (2016)
	Toothache	Eastern Ghat of Northern Andhra Pradesh, India	Stem, roots	—	Venkaiah et al. (2020)

Note: — indicates not mentioned in the retrieved literature.

ether, chloroform, and butanol. Their fractions were then subjected to analyses using MS, 1H-NMR, and 13C-NMR to reveal the presence of coumaperine, piperolactam A, bisdemethoxycurcumin, (+)-aphanamol I, demethoxycurcumin, *N*-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, 1-[1-oxo-5 (3,4-methylenedioxyphenyl)-2E,4E-pentadienyl] -pirrolidine, 1-[1-oxo-5 (3,4-methylenedioxyphenyl)-2E-pentenyl]–pirrolidine, 1-[1-oxo-9 (3,4-methylene dioxyphenyl)-2E,8Enonadienyl]-pyrrolidine, (R)-(−)-turmerone, and octahydro-4-hydroy-3alpha-me thyl-7-methylenealpha-(1-methylethyl)-1*H*-indene-1-methanol were identified (Liu, Jiang, Chen, Zhang, & Ma, 2009). A piperine derivative GB-N was also identified from the ethanol extract of the whole plant that improved hyperlipidaemia in rats (Bao, Bai, & Borijihan, 2012). A number of flavonoids such as catechin, epicatechin, quercetin, myricetin, kaemferol, apigenin, luteolin, and naringenin were identified from the whole plant (Liu et al., 2009; Mustafa, Hamid, Mohamed, & Bakar, 2010).

5.2 | Phytochemicals identified from the stem

The oil from the stem was composed of mono- (69.2%) and sesquiterpene (25.6%). A number of volatile oil components such as camphene, caryophyllene, caryophyllene oxide, decanal, eucalyptol, gurjunene, limonene, linalool, pentadecane, terpineol, terpinolene, and so on are identified from the stem of *P. longum* (Varughese, Unnikrishnan, Deepak, Balachandran, & Rema Shree, 2016).

5.3 | Phytochemicals identified from the leaf

The leaves of *P. longum* are dominated by essential oils. Bhuiyan et al. have isolated 70 volatile components from the leaf of *P. longum* such as Bornyl acetate, cadinene, camphene, caryophyllene, cubenol, cyclohexane, elemol, humulene, linalool, nerolidol, verrucarol, α-himachalene, β-elemene, β-selinene, δ-guaiene, α-eudesmol, α-humulene, α-cadinol, α-muurolene, β-eudesmol, β-myrcene, and δ-cadinol (Bhuiyan, Begum, & Anwar, 2008).

5.4 | Phytochemicals identified from the inflorescence

A report of 30 volatile components were reported from the *P. longum* inflorescences using the gas chromatography–mass spectrometry (GC–MS) electron impact ionization method. The compounds were caryophyllene, nerolidol, cinnamyl acetate, α-pinene, eugenol, acetate, acetate, humulen-(v1), 2-heptanol, phytol, pinene, α-elemene, and limonene (Bhuiyan et al., 2008). Miscellaneous compounds such as n-eicosane; n-heneicosane; n-hexadecane; n-heptadecane; ρ-methoxyacetophenone; n-octadecane; and β-phenylethanol were also identified from the *P. longum* inflorescence (Handa, Sharma, & Nigum, 1963).

5.5 | Phytochemicals from the fruits

P. longum fruit contains a number of phytochemicals, mostly amide alkaloids, lignans, ester, organic acid, sterol, and volatile oils which are identified and quantified by many researchers. The fruits were also positive for the presence of volatile oil, starch, proteins, alkaloids, saponins, carbohydrates, and amygdalin, while they were negative for tannins (Bedi & Atal, 1971; Dutta, Banerjee, & Roy, 1975). Boa et al. measured the alkaloid piperine yield (16.58 ± 0.02 mg/g) from the dried fruit of *P. longum* and the yield of piperlonguminine was found to be 0.80 ± 0.02 mg/g (Bao et al., 2012). Along with these two compounds, pipernonaline and piperoctadecalidine were also isolated from the fruit and showed antiplatelet activity (Park, Son, Park, Kim, & Lee, 2007). Dehydropipernonaline and tetrahydropiperine were also identified from the *P. longum* fruit extracts (Madhusudhan & Vandana, 2001; Shoji et al., 1986). The compound sarmentine, isolated from the ethanol solution fruit extract, was found to be phytotoxic whereas pipyahyine from a petroleum ether fruit extract exhibited larvicidal activity against *Culex quinquefasciatus* (Huang, Morgan, Asolkar, Koivunen, & Marrone, 2010; Madhu, Vijayan, & Shaukath, 2011). MS of the methanol extract of *P. longum* fruit revealed the presence of alkamides such as piperine, pipercide, retrofractamide C, pellitorin, piperloein B, guineesine, dehydroretrofractamide C, pipernonaline, dehydropipernonaline, and P(2E,4Z,8E)-*N*-[9-(3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl]-piperidine. Among these, pipernonaline, dehydropipernonaline, and piperloein B were found to produce antiproliferative activity against the IL-6 cancer cell line (Lee et al., 2010). Piperlongumamide A, B, and C along with isopiperine, chavicine, brachystamide B, guineensine, piperchabamide B, (2E,4E)-*N*-dodecadienoylpiperidine, and piperolein B also isolated from the fruit showed cytotoxic property against human lung cancer, human leukaemia, breast cancer, rectal cancer, and liver cancer (Yang et al., 2013). Petrol fraction and ethanol extract of *P. longum* fruit also possessed a number of alkaloids such as piperlongumine, piperlonguminine, norcepharadione B, cepharadlone B, cepharanone B, cepharadlone A, aristolactam AH, piperolactam A and B, and piperadione (Desai, Prabhu, & Mulchandani, 1988). *Piper longum* fruits have been reported to contain a number of compounds in their volatile oils such as β-pinene, eugenol, 3-carene, β-elemene, βcaryophyllene, germacrene D, cubenol, zingiberene, cadina-1,4-diene, D-limonene, and β-eudesmol identified by GC–MS from the solid phase microextraction and microwave heating methods (Liu et al., 2007). Around 44 volatile oil components were identified from *P. longum* fruit that produced 0.6% oil (Shankaracharya, Jaganmohan Rao, Pura Naik, et al., 1997; Tewtrakul et al., 2000). Varughese et al. found that the fruit oil contains monoterpene hydrocarbons (71.5%) with β-pinene as the single largest component (Varughese et al., 2016). A number of phenolic and flavonoid compounds were isolated and identified from *P. longum*. The presence of flavonoid compounds such as quercetin, caffeic acid, and kaempferol and phenolic compounds such as bavachin, bakuchiol, and isobavachalcone were identified from the fruits of *P. longum* (Ohno et al., 2010).

5.6 | Phytochemicals identified from the seed

Lignans such as sylvatine and dieudesmin were reported in the seeds, as well as iso-fatty acids like palmitic, hexadecenoic, stearic, linoleic, oleic, arachidic, and behenic acids, along with higher saturated acids (Bedi & Atal, 1971; Dutta et al., 1975). The presence of lignans including sesamin, sylvatin, and diaeudesmin were reported from the petroleum ether extract of *P. longum* seeds (Dutta et al., 1975). Lignin molecules such as (+)-asarinine and pluviatilol were also found in the seeds (Parmar et al., 1997).

5.7 | Phyochemicals identified from the roots

The result showed that the root oil was dominated by monoterpene hydrocarbons (62.0% of the total oil) and sesquiterpene hydrocarbons (27.5% of the total oil) (Varughese et al., 2016). Essential oils camphene, caryophyllene, cis-ocimene, eucalyptol, humulene, limonene, pentadecane, tridecane, α-phellandrene, α-pinene, β-elemene, β-myrcene, β-phellandrene, β -pinene, δ-elemene, δ-cadinol; amide alkaloid such as piperlongumine, cepharadione A, cepharanone B, aristolactam AII, norcepharadione B, piperolactum A, piperadione, terpenes like dihydrocarveol, zingiberene, ρ-cymene, terpinolene are also identified from *P. longum* roots in various investigations (Chatterjee & Dutta, 1967; Desai et al., 1988; Dutta, Banerjee, Sil, & Roy, 1977; Liu et al., 2009).

Varughese et al. found 0.026%, 0.054%, 0.1%, and 0.077% volatile oils produced from the stem, root, fruit, and leaf respectively which also contained 36, 38, 29, and 37 chemical constituents, respectively (Varughese et al., 2016). A recent study identified 159 phytochemicals categorized into 26 different classes namely carboxylic acids and derivatives, isoflavonoids, cinnamic acids and derivatives, napthalenes, phenanthrenes and derivatives, oxanes, phenol ethers, organic nitrogen compounds, phenylpropanoic acids, pteridines and derivatives, benzodioxole pyridines and derivatives, and so on (Choudhary & Singh, 2017).

Phytochemicals reported from different parts of *P. longum* are summarized in Table 2. Figure 5 presents the structures of phytochemicals reported from *P. longum* (obtained from www.ChemSpider.com and www.PubChem.com).

6 | PHARMACOLOGICAL ACTIVITIES

6.1 | Antiproliferative, anticancer, and antitumour activities

Cancer is still an aggressive killer worldwide despite considerable efforts are put into treatment procedures, stratagem, and researches. Though novel synthetic chemotherapeutic agents are currently in clinical use the strategies have not succeeded in attaining expectations till date despite the considerable cost of their development (Solowey et al., 2014). Therefore, there is a constant exigency to develop new, effective, and affordable anticancer drugs (Coseri, 2009). About 60% of the drugs currently used in the treatment of cancer are natural product-derived (Gordaliza, 2007). Pipernonaline, a piperine derivative isolated from *P. longum* was tested on androgen-independent human prostate cancer PC-3 cells and androgen dependant LNCaP prostate cells. The growth inhibition of PC-3 cells upon pipernonaline administration occurred in a dose-dependent manner associated with the accumulation of sub-G_1 and G_0/G_1, down-regulation of CDK2, CDK4, cyclin D1, and cyclin E, and up-regulation of cleavage of procaspase-3/poly (ADP) ribose polymerase (PARP). Apoptosis was exhibited through reactive oxygen species (ROS) production, depolarization of the mitochondrial membrane, and Ca^{2+} homeostasis leading to the downstream processes including activation of caspase-3 and cleavage of PARP in PC-3 cells (Lee et al., 2013).

In another study, to validate the antiproliferative activity of *P. longum*, the ethanol extract of the fruits was used to assess cell viability by WST-1 assay, apoptosis induction by nuclear staining, annexin V binding assay, terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) staining, and tetramethylrhodamine methyl ester (TMRM) staining employing different human cell lines. The efficacy and toxicity were measured in vivo in CD-1 nu/nu immunocompromised Balb/C mice. The result indicated that the *P. longum* extract facilitated caspase-independent apoptosis in cancer cells via targeting the mitochondria, causing disruption of the mitochondrial membrane potential (MMP) and an enhancement in ROS generation with no influence on the noncancerous cells. The in vivo studies showed that oral administration of the extract arrested the growth of colon cancer tumours in immunocompromised mice, without any related toxicity (Ovadje et al., 2014). In vitro anticancer potential of different solvent extracts (chloroform, benzene, ethyl alcohol, and aqueous) of *P. longum* were evaluated for their effects on human cancer cell lines (DU-154 prostate, A-594 lungs, THP-1 leukaemia, IGROV-1 ovary, andMCF-7 breast) via disruption of cell cycle progression. The highest toxicity (91–95%) was observed on A-594 cell lines using hexane, benzene, and acetone extracts. Hexane extract displayed 90–92% cytotoxicity against A-594, THP-1, IGR OVI-1, and MCF-7 cell lines (Sharma, Kumar, Chashoo, Saxena, & Pandey, 2014). Methanol extract of the *P. longum* fruits showed 100% toxicity on Dalton's lymphoma ascites (DLA) cells and Ehrlich ascites carcinoma (EAC) cells in a dose-dependent manner. The extract also demonstrated cytotoxicity against L929 cells. Inhibition of solid tumour development was observed in DLA cells induced mice with administration of alcoholic extract of *P. longum* alongside an increase in the life span of mice bearing Ehrlich ascites carcinoma tumour (Sunila & Kuttan, 2004). Hydroalcoholic extract of fruits also exhibited antiproliferative activity towards human colon cancer Colo205 cell line (Gaidhani et al., 2013). Ethanol extract of the fruits, supercritical fluid extract (SE) and isolated compounds from the plant exhibited significant cytotoxicity, reduced colony formation, inhibited cell migration, and promoted apoptosis through increased cleaved PARP and ratio of Bax/Bcl-2 in HepG2, HeLa, and SKOV-3 human cancer cell lines (Guo et al., 2019). In vitro anticancer activity of *P. longum* root extract was reported on LN-CAP human prostate cancer cells in a concentration

TABLE 2 Phytochemistry of *P. longum*

Plant parts	Compounds	References
Whole plant	**Amide alkaloids**: Aphanamol; bisdemethoxycurcumin; coumaperine; demethoxycurcumin; piperolactam A; turmerone; 1-[1-oxo-5(3,4-methylenedioxyphenyl)-2E,4E-pentadienyl]-pyrrolidine; *N*-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine; 1-[1-oxo-5 (3,4-methylenedioxyphenyl)-2E-pentenyl]-pyrrolidine; 1-[1-oxo-9 (3,4-methylene dioxyphenyl)-2E, 8 enonadienyl]-pyrrolidine; octahydro-4-hydroy-3alpha-methyl-7 methylenealpha-(1-methylethyl)-1*H*-indene-1-methanol; *N*-isobutyl-5-(3,4-methylenedioxyphenyl)-2E,4E-pentadienamine **Flavonoids**: Catechin; epicatechin; quercetin; myricetin; kaemferol; apigenin; luteolin; naringenin	Liu et al. (2009), Mustafa et al. (2010), and Bao et al. (2012)
Stem	**Essential oil**: 2-undecanone; 8-isopropenyl-1,5-dimethylcyclodeca-1,5-diene; bornyl acetate; camphene; caryophyllene; caryophyllene oxide; decanal; eucalyptol; gurjunene; limonene; linalool; pentadecane; terpineol; terpinolene; terpinyl acetate; trans-ocimene; tridecane; α-phellandrene; α-pinene; β-myrcene; β-patchoulene; β-phellandrene; β-pinene; δ-elemene	Varughese et al. (2016)
Leaves	**Essential oil**: (z)-â-farnesene; 1-methylhexyl acetate; 1-tridecene; 26,27-dinorergosta-5,23-dien-3-ol, (3. Beta.)-; 2-acetoxytetradecane; 2-butenal 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-; 2-methoxybenzyl acetate; 2-nonanone; 2-tridecanone; 2-undecanone; 3-heptane; 3-heptene, 7-phenyl-; 3-tert-Butylphenol; 3-tridecen-1-yne, (Z); 8-isopropenyl-1,5-dimethylcyclodeca-1,5-diene; 8-pentadecanone; 8-tetradecyn-1-ol; 9,12,15-octadecatrien-1-ol, (Z,Z,Z)-; benzaldehyde, 2,4,5-trimethoxy-; benzene, (3,3-dimethyl-4-pentenyl)-; benzene, 5-heptenyl-; benzyl benzoate; bornyl acetate; butylated hydroxytoluene; cadinene; camphene; carane 4,5-epoxy-trans; caryophyllene; caryophyllene oxide; caryophyllene-(i1); cubenol; curcumene; cyclohexane, 2-ethenyl-1,1-dimethyl-3-methylene-; cyclohexanone, 2-cyclohexylidene-; cyclooctene, 1,2-dimethyl-; delta.-cadinol; dodecanal; elemol; glaucyl alcohol; guaiene; gurjunene; heptadecane; humulene; isobornyl acetate; isocaryophillene; l-ascorbic acid 2,6-dihexadecanoate; ledene alcohol; ledol; linalool; lineoleoyl chloride; methyl (z)-5,11,14,17-eicosatetraenoate; methyl 3,4-dimethoxycinnamate; naphthalene; methylconiferylaldehyde; 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-; naphthalene; decahydro-neoisomenthol; nerolidol; nerolidol acetate; nonane, 5-propyl-; octacosane; patchoulane; retinal; tetracyclo[6.3.2.0(2,5).0(1,8)]tridecan-9-ol, 4,4-dimethyl-; tetradecane; thujone; thujopsene; tigogenin lactone acetate; trans-nerolidol; tridecane; triquinacene, 1,4-bis(methoxy)-; verrucarol; ylangene; z-ocimene; α-cadinol; α-caryophyllene; α-cubebene; α-himachalene; β-elemene; β-selinene; δ-guaiene; α-eudesmol; α-humulene; α-cadinol; α-muurolene; α-pinene; β-cubebene; β-elemene; β-eudesmol; β-myrcene; δ-cadinol; γ-elemene; γ-muurolene	Varughese et al. (2016) and Bhuiyan et al. (2008)
nflorescence	**Essential oil**: 1,6,10,14-hexadecatetraen-3-ol, 3,7,11,15-tetramethyl-, (E,E)-; 1,6,10-dodecatriene, 7,11-dimethyl-3-methylene-, (Z)-; 1*H*-indene, 1-ethylideneoctahydro-7a-methyl-, cis-; 2,4-dodecadienal, (E,E)-; 2-heptanol, acetate; azulene, 1,2,3,4,5,6,7,8-octahydro-1,4-dimethyl-7-(1-methylethenyl)-, [1S-(1α,4 α,7 α)]-; benzenepropyl acetate; benzyl benzoate; butylated hydroxytoluene; caryophyllene; cedrene; cinnamaldehyde, (e)-; cinnamyl acetate; cyclopropanecarboxylic acid; nonyl ester; eugenol; humulen-(v1); limonene; linalool; lineoleoyl chloride; nerolidol, acetate; n-hexadecanoic acid; phytol; pinene; zingiberene; α-caryophyllene; α-cubebene; α-farnesene; β-pinene; β-seline; γ-elemene; γ-nonanolactone **Miscellaneous compounds**: n-eicosane; n-heneicosane; n-hexadecane; n-heptadecane; ρ-methoxyacetophenone; n-octadecane; β-phenylethanol	Bhuiyan et al. (2008) and Handa et al. (1963)
Fruit	**Amide alkaloids**: 3β,4α-dihydroxy-1-(3-phenylpropanoyl)-piperidine-2-one; (2E, 4E, 14Z)-6-hydroxyl-*N*-isobutyleicosa-2,4,14-trienamide; desmethoxypiplartine; (Z)-12-octadecenic-alpha-glycerol monoester; piperine; β-setosterol; daucosterol; ethyl 3′,4′,5′-trimethoxycinnamate; retrofractamide C; pipercide; pellitorine; dehydroretrofractamide C; guineensine; dehydropipernonaline; (2E,4Z,8E)-*N*-[9- (3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl] piperidine; pipernonaline; pipyahyine; tetrahydropiperine; dehydropipernonaline; piperlongumamides A–C; isopiperine; chavicine; piperlonguminine; brachystamide; piperchabamide; (2E,4E)-*N*-dodecadienoylpiperidine; piperolein B; sarmentine; longamide **Lignan**: Pluviatilol; sesamine; asarinine **Essential oil**: 1-methylhexyl acetate; 2-nonanone; 2-tridecanone; 2-undecanone; 7-epi-α-selinene; 8-heptadecane; 9-octadecane; ar-curcumene; bisabolene; camphene; caryophyllene; cis-ocimene; decanal; germacrene D; limonene; linalool; nonadecane; pentadecane; terpinolene; α-humulene; α-phellandrene; α-pinene; β-caryophyllene; β-myrcene; β-pinene; β-selinene; β-bisabolene	Handa et al. (1963), Chatterjee and Dutta (1966), Sharma, Rathore, and Kumar (1983), Shoji et al. (1986), Kirtikar and Basu (1987), Koul, Taneja, Agarwal, and Dhar (1988), Ke, Changxiang, Dezu, and Yu (1996), Tewtrakul et al. (2000), Madhusudhan & Vandana, 2001; Kumar et al. (2005), Bhuiyan et al. (2008), Huang et al. (2010), Madhu et al. (2011), Yang et al. (2013), Yang et al. (2013), Jiang, Liu, Huang, and Huang (2013), Varughese et al. (2016)

TABLE 2 (Continued)

Plant parts	Compounds	References
	Phenolics: Bavachin, bakuchiol, and isobavachalcone	
	Flavonoids: Quercetin, caffeic acid, and kaempferol	
	Ester: Eicosanyl-(E)-coumarate; Z-12-octandecenoic-glycerol-monoester; tridecyl-dihydro-coumaarate	
	Organic acids: Palmitic acid; tetrahydropiperic acid	
	Sterol: Sitosterol	
	Miscellaneous compounds: D-asparatic acid; DL- serine; L-tyrosine	
Seed	**Lignan**: Sylvatine; diaeudesmin; (+)-asarinine; (+)-diaeudesmin	Atal and Banga (1962), and Dutta et al. (1977)
Root	**Amide alkaloid**: Piperlongumine; cepharadione A, B, cepharanone B; aristolactam AII; norcepharadione B; 2-hydroxy-1-methoxy-4H-dibenzo[de,g]quinoline-4,5(6H)-dione; piperolactum A, B; piperadione **Essential oil**: 1-pentadecene; 2-undecanone; 8-isopropenyl-1,5- dimethylcyclodeca-1,5-diene; 9-eicosyne; bornyl acetate; camphene; caryophyllene; caryophyllene oxide; cis-ocimene; eucalyptol; heptadecane; humulene; limonene; pentadecane; terpinyl acetate; trans-ocimene; tridecane; α-phellandrene; α-pinene; β-elemene; β-myrcene; β-patchoulene; β-phellandrene; β-pinene; δ-elemene; δ-cadinol; **Terpene**: Dihydrocarveol; a-thujene; zingiberene; ρ-cymene; terpinolene **Miscellaneous compounds**: Cysteine	Handa et al. (1963), Chatterjee and Dutta (1967), Dutta et al. (1977), Desai et al. (1988), Liu et al. (2009), and Varughese et al. (2016)

and time-dependent manner (Deeparani & Jayakumari, 2019). *Piper longum* root extract was also recorded to inhibit the growth of MCF-7 human breast cancer cells growth (Urolagin & Jayakumari, 2018). *Piper longum* was also used to evaluate the antiproliferative activity or cytotoxicity on a human liver cancer cell, Hep G2. The methanol extract of *P. longum* was found to possess antiproliferative potency (Aung, Myint, Myint, & Than, 2020).

In a study, intracerebral implantation of C6 glioma cells in albino Wistar rats was performed to induce glioma which showed increased levels of kinase (CK), 5′ nucleotidase (5′ND) and acetylcholine esterase (AChE). Pre-administration of *P. longum* leaves, extracted in petroleum ether significantly attenuated these alterations and was proved to be a potent anticancer agent in glioma-induced rats (Subramanian, Poongavanam, & Vanisree, 2010).

Antiproliferative, anticancer, and antitumour activities of the plant on various human cancer cell lines are mainly mediated by inhibition of oxidative stress, induction of apoptosis, disruption of mitochondrial function, and regulation of biochemical markers. The solvent extracts of various plant parts along with piperine and pipernonaline-rich fractions exhibited anticancer properties. The reports also demonstrate selective cytotoxicity of *P. longum* towards various cancer cells besides providing anticancer properties, as evidenced by Ovadje et al., 2014, and Sunila & Kuttan, 2004, who recorded the decline in tumour size, enhancement in the life span of cancer-affected mice and arresting tumour growth in immunocompromised mice. Majority of anticancer studies involved cellular and animal models analysing the cytotoxicity and pro-apoptotic activities of the crude extracts/fractions. In addition, no ethnopharmacological relevance of its anticancer activities was retrieved from the literature. Therefore, the preliminary nature of the in-vitro anticancer investigations is mostly limited to human cancer cell lines in reporting the cytotoxicity and pro-apoptotic activities of the extracts and the phytochemicals. Therefore, more clinical trials are needed to validate the anticancer properties of the plant and its phytochemicals in humans especially targeting the relevant genes and pathways involved in autophagy. Antiproliferative, anticancer, and antitumour activities of *P. longum* are summarized in Table 3.

6.2 | Neuro-pharmacological activity

Mental, neurological, and behavioural disorders are common in all countries, which cause immense suffering across the world. People with these disorders often suffer social isolation, poor life quality, and elevated mortality rate. Habituation, dependence, and probable addiction are among the many shortcomings of modern synthetic psychopharmacological drugs. Abrupt discontinuation of long-term therapy with these agents often causes serious withdrawal symptoms. Therefore, modern society is constantly exploring the efficacies of traditional herbal remedies, particularly those found effective in controlled studies and which in many instances displayed even better galenic properties than conventional medicines. In addition, ethnopharmacological claims of using this plant against neurological disorders and as

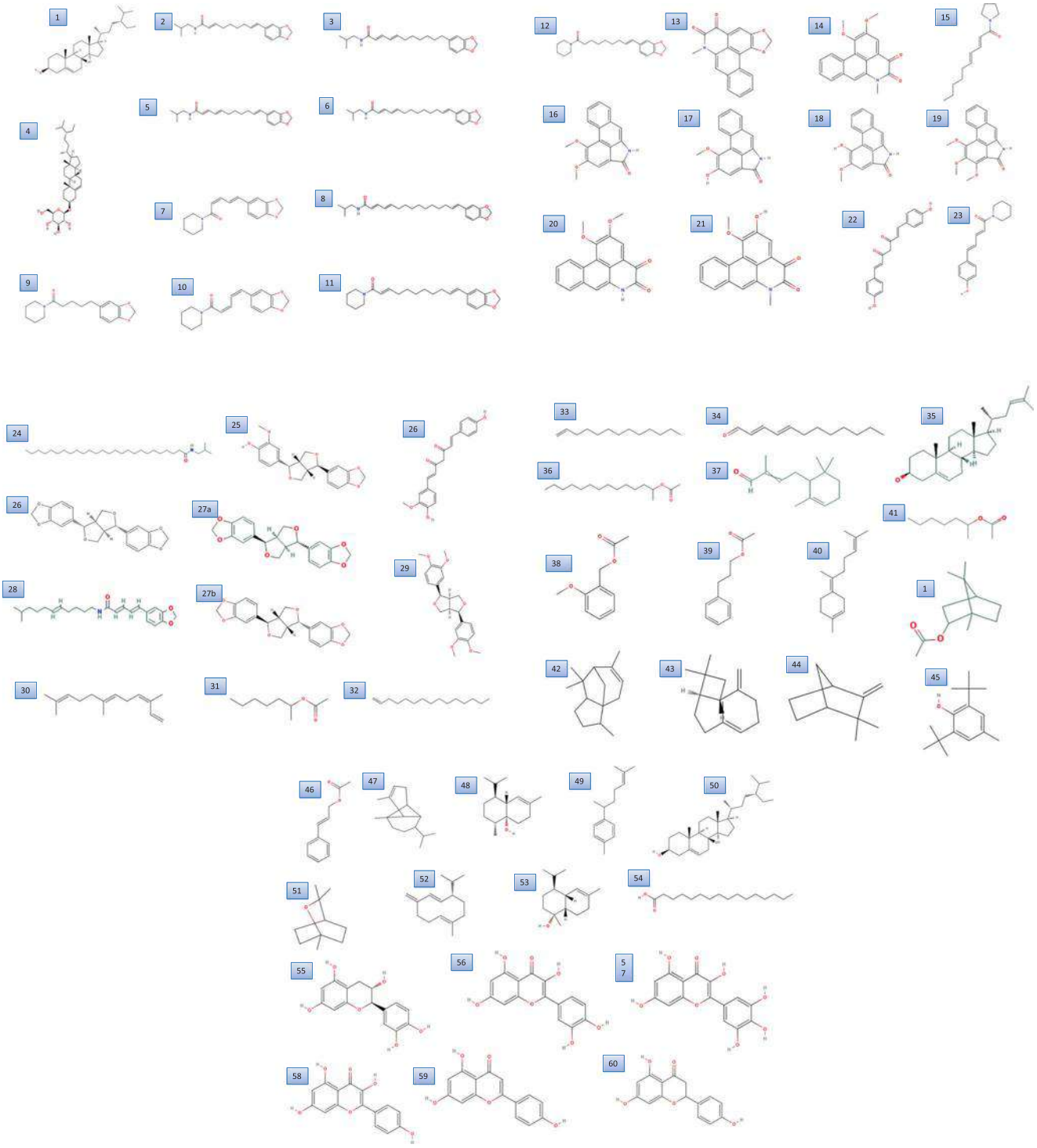

FIGURE 5 Structures of phytochemicals reported from *P. longum* (obtained from www.ChemSpider.com and www.PubChem.com) (1) β-sitosterol, (2) retrofractamide C, (3) dehydroretrofractamide C, (4) daucosterol, (5) pipercide, (6) guineensine, (7) isopiperine, (8) brachystamide B, (9) chavicine, (10). piperchabamide B, (11). piperolein B, (12). cepharadione A, (13) cepharadione B, (14) sarmentine, (15) cepharanone A, (16) aristolactam AII, (17) piperolactum C, (18) piperolactum A, (19) norcepharadione B, (20) piperadione, (21) bisdemethoxycurcumin, (22) coumaperine, (23) longamide, (24) pluviatilol, (25) demethoxycurcumin, (26) sesamin, (27a) asarinine, (27b) (−)-asarinine, (28) sylvatine, (29) diaeudesmin, (30) (Z,E)-α-farnesene, (31) 1-methylhexyl acetate, (32) 1-pentadecene, (33) 1-tridecene, (34) 2,4-dodecadienal, (E,E)-, (35) 26,27-dinorergosta-5,23-dien-3-ol, (3β)-, (36) 2-acetoxytetradecane, (37) 2-butenal, 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (38) 2-heptanol, acetate, (39) 2-methoxybenzyl acetate, (40) benzenepropyl acetate, (41) bisabolene, (42) bornylacetate, (43) butylated hydroxytoluene, (44) cadinene, (45) caryophyllene, (46) camphene, (47) butylated hydroxytoluene, (48) cinnamyl acetate, (49) copaene, (50) cubenol, (51) sitosterol, (52) eucalyptol, (53) germacrene D, (54) δ-cadinol, (55) catechin, (56) quercetin, (57) myricetin, (58) kaemferol, (59) apigenin, (60) naringenin

TABLE 3 Antiproliferative, anticancer, and antitumour activities of *P. longum*

Parts used (solvents/ fractions)	Effective phytochemicals	Tested concentration(s)	Experimental design	In vitro/ in vivo	Cell line/animal model	Results/mechanism of action	References
Methanol extract of fruit	Piperine	10 mg/dose/animal, (1.14 mg/dose/ animal)	Trypan blue dye exclusion method, MTT assay, determination of tumour growth	Both in vitro and in vivo	Dalton's lymphoma ascites (DLA) and Ehrlich ascites carcinoma (EAC) cells, L929 cells, DLA and EAC-induced Balb/C mice	100% toxicity (DLA and EAC cells), cytotoxicity (L929 cells), tumour development in DLA cells-induced mice ↓, life span in EAC cell-induced mice ↑	Sunila and Kuttan (2004)
Ethyl acetate, methanol, and aqueous extract		10 μg/ml, 50 μg/ml, and 100 μg/ml	MTT assay	In vitro	Human lung epithelial adenocarcinoma cell line (HCC-827)	Dose-dependent inhibition of cancerous cells, distortion, and disorganization of cytoskeleton ↑	Sawhney, Painuli, and Chauhan (2011)
Fruit extract	Pipernonaline	30–90 μM	MTT assay	In vitro	Prostate cancer PC-3 cells	ROS-mediated apoptosis, disruption of mitochondrial function, Ca^{2+} homeostasis, activation of caspase-3 and cleavage of PARP↑	Lee et al. (2013)
Hydro-alcoholic extract of fruits	—	10, 20, 40, and 80 μg/ ml	Sulforhodamine B (SRB) assay	In vitro	14 different human cancer cell lines	Antiproliferative activity against only colon cancer cell line Colo 205	Gaidhani et al. (2013)
Fruit hexane, benzene, acetone, ethyl acetate, ethyl alcohol, chloroform, and aqueous extracts	—	50 mg/kg/day	WST-1 assay, nuclear staining, annexin V binding assay, TUNEL staining, tetramethylrhodamine methyl ester (TMRM) staining, toxicity and efficacy tests	Both in vitro and in vivo	Malignant melanoma G-361, human colorectal cancer HT-29 and HCT116, ovarian adenocarcinoma OVCAR-3, pancreatic adenocarcinoma BxPC-3, colon mucosa NCM 460 cell line and in vivo Balb/C mice and CD-1 nu/nu immunocompromised mice	Caspase-independent apoptosis, dissipation of the MMP and ROS production ↑	Ovadje et al. (2014)
Hexane, ethyl acetate, acetone, chloroform, benzene, ethyl alcohol, and aqueous extracts of fruits	—	100 μg/ml	Nuclear staining, annexin V binding assay, TUNEL staining	In vitro	DU-154 prostate, A-594 lungs, THP-1 leukaemia, IGR OVI-1 ovary, MCF-7 breast	Cytotoxicity varying from 82% to 94% and cell cycle inhibitory effect ↑	Sharma, Kumar, et al. (2014)
Ethanol extract of fruits, supercritical fluid extract (SE), isolated compounds	-	Upto 100 μg/ml	MTT assay, colony forming assay, Hoechst 33 258 staining assay	In vitro	HepG2, HeLa and SKOV-3	Significant cytotoxicity ↑, colony formation ↓, cell migration ↓, apoptosis ↑, cleaved PARP and ratio of Bax/Bcl-2 ↑	Guo et al. (2019)

(Continues)

TABLE 3 (Continued)

Parts used (solvents/fractions)	Effective phytochemicals	Tested concentration(s)	Experimental design	In vitro/in vivo	Cell line/animal model	Results/mechanism of action	References
Ethanol extract of roots	-	20–320 μg/ml	MTT assay	In vitro	MCF-7 breast carcinoma cells	14–90% growth ↓, IC_{50} value of 120.5 μg/ml	Urolagin and Jayakumari (2018)
Ethanol extract of roots	-	0–640 μg/ml	MTT assay	In vitro	LN-CAP human prostate cancer cells	10–58% growth ↓, IC_{50} value of 531.3 μg/ml	Deeparani and Jayakumari (2019)
Methanol extract of fruits	-	0–300 μg/ml	MTT assay	In vitro	Human liver cancer cell Hep G2	Antiproliferative potency ↑, IC_{50}value of 87.7 μg/ml	Aung et al. (2020)
Petroleum ether extract of leaves		20 mg/kg body weight	Histopathological and biochemical analyses	In vivo	C6 glioma induced albino mice	Level of ipid peroxides, LDH, CK, 5′ND, and AchE ↓	Subramanian et al. (2010)

neuroprotective and psychoactive have been supported by pharmacological evidence. The following section depicts the plethora of neuroprotective and psychoactive properties of *P. longum* which are also tabulated in Table 4.

6.2.1 | Anti-Alzheimer's disease activity

Alzheimer's disease (AD) is a common neurodegenerative disorder characterized by cerebral amyloid deposits, synaptic dysfunction in the brain, neurofibrillary tangle formation, and progressive cognitive impairment (Sosa-Ortiz, Acosta-Castillo, & Prince, 2012). Sirtuin 1 (Sirt1), an unusual target for aging and aging-associated diseases has been shown to modulate synaptic plasticity and memory formation (Gao et al., 2010) and attenuate neurodegenerative disorders, including AD (Qin et al., 2006). Piperlongumine isolated from *P. longum* fruit activated the deacetylase ability of Sirt1 in hippocampal neurons and attenuated cytotoxicity induced by intra-neuronal Aβ1-42 expression in vitro. Oral administration of piperlongumine reduced the occupied area of β-amyloid in the parietal cortex of APP/PS1 mice. The treatment also decreased the activated microglia and astrocytes in the cortex and significantly increased the vesicular glutamate transporter 1 (VGLUT1) in the hippocampus of APP/PS1 mice suggesting the therapeutic potential of *P. longum* to attenuate AD-like pathology (Go et al., 2018). Acetylcholinesterase (AChE) inhibitors are thought to be the best therapeutic option for AD to date. Dichloromethane extract of the fruits was found to inhibit AChE which was observed via thin layer chromatography (TLC)-bio-autography (Khatami et al., 2020).

Application of *P. longum* against AD has mostly been correlated to its ability to reduce dementia, restore cognitive functions and reduce the symptoms. A detailed study is needed to find out the modulation of cerebral function and related signal transduction mechanisms following its administration.

6.2.2 | Anti-Parkinson's disease activity

Parkinson's disease (PD) is the most common chronic neurodegenerative disease, characterized clinically by resting tremor, rigidity, bradykinesia, postural instability, and loss of pigmented dopaminergic neurons in the substantia nigral pars compacta (SNpc) of the midbrain attendant projections to the putamen. Accumulation of intracellular protein aggregates, Lewy bodies, and Lewy neurites, composed primarily of the protein α-synuclein is also the major hallmarks of this disease (Braak & Del Tredici, 2008). Neuroprotective effect of the extract of *P. longum* seeds, prepared in 85% ethanol, containing piperine and piperlongumine was observed in 1-methyl-4-phenyl-1,-2,3,6-tetrahydropyridine (MPTP)-induced PD in C57BL/6 mice which was probably mediated by antioxidation mechanism. The extract significantly increased the levels of dopaminerigic (DA) neurones and GABA identified by UPLC-MS/MS analysis, increased glutathione (GSH) level and superoxide dismutase (SOD) activity, and decreased the lipid peroxidation of malondialdehyde (MDA) in mice (Bi

TABLE 4 Neuroprotective and psychoactive properties of *P. longum*

Activities	Plant parts/extracts	Effective phytocompounds	Tested concentrations	In vitro or in vivo experiment	Cell line/animal model	Experimental design	Results with mechanism of action	References
Anti-Alzheimer's disease activity	Fruits	Piperlongumine	50 mg/kg/day	Both in vitro and in vivo	Murine hippocampal neuroblastoma HT22 and HT22-ARE cells and APP/PS1 mice	Sirt1 deacetylation assay, Y-maze alternation, immunohistochemistry	Sirt1 deacetylation ↑, cytotoxicity by intraneuronal Aβ1-42 in hippocampal neurons ↓, area of β-amyloid in parietal cortex ↓, activated microglia and astrocytes in the cortex ↓, VGLUT1 in mice hippocampus ↑	Go et al. (2018)
	Dichloromethane extract of fruits	–	25 μl (3.1 to 400 μg/ml in 10% DMSO)	In vitro using acetylcholinesterase (AChE)	–	TLC-bio-autography, bioassay-guided phytochemical investigation	Effective enzyme inhibitory effect	Khatami et al. (2020)
Anti-Parkinson's disease activity	Ethanol extract of fruits	–	50 mg/kg	In vivo	6-OHDA-induced PD in rats	Apomorphine-induced rotation, rotary rod tests, TH, SOD, GSH-Px, GSH, catalase, MDA, NO and NOS level determination	Behavioural abnormality ↑, TH cell numbers ↑, SOD, GSHPx, catalase and GSH activity ↑, NOS, MDA and NO content ↓	Zheng et al. (2014)
	Ethanol extract of fruit	Piperine and piperlongumine	30, 60, and 120 mg/kg	In vivo	MPTP-induced of PD in C57BL/6 mice	Open field test, UFLC-MS/MS, TH-immunohistochemistry assay, and western blotting	Total movement time and distance ↑, neuroprotective effects ↑, properties in dopaminergic neurons ↓	Bi et al. (2015)
	Ethanol extract of fruits	–	25, 50 and 75 mg/kg	In vivo	LPS-induced PD in Sprague–Dawley rats	Rotational behaviour, rotarod test and open-field test, IL-6, IL-1β, and TNF-α immunoassay, measurement of ROS and NO	Survival rate of TH-ir neurons ↑, over-activated microglial cells were ↓, inflammatory cytokines ↓, excessive production of ROS and NO ↓	He et al. (2016)
	Fruit	Piperine and piperlonumine	12.5 mg/kg and g 25 mg/kg	In vivo	Rotenone-induced motor impairment in Wistar rats	Behavioural studies, MTT and LDH release assays, cell death, and measurement of MMP detection	Improvement of rotenone-induced motor deficits ↑, ROS production ↓, stabilized MMP, inhibited mPTP	Wang et al. (2016)
Antidepression activity	Extract of fruits	Piperine	1, 3, 9 mg/kg	In vivo	ICR mice and mitochondrial fraction from brain	Open field test, tail suspension test, MAO activity measurement assay	MAO-A ↓ (IC_{50} value: 20.9 mM) and MAO-B ↓ (IC_{50} value: 7.0 mM); immobility times ↓	Lee et al. (2005)
	Fruits extract	Methylpiperate, guineensine and piperlonguminine	–	In vivo	Mitochondrial fraction from ICR mouse brain	MAO activity measurement assay	MAO ↓ (by methylpiperate and guineensine, IC_{50} values of 3.6 and 139.2 μM, respectively), MAO-B ↓ (by methylpiperate)	Lee et al. (2008)
	Volatile oil from fruit	–	10 mg/kg	In vivo	Albino mice	Forced swim test	Immobility ↓ (compared to fluoxetine)	Khan (2015)

(Continues)

TABLE 4 (Continued)

Activities	Plant parts/extracts	Effective phytocompounds	Tested concentrations	In vitro or in vivo experiment	Cell line/animal model	Experimental design	Results with mechanism of action	References
	Methanol extract of fruit and root	Piperine and piperlongumine	4 mg/kg doses for 11 days	In vivo	Adult male Swiss albino mice	Tail suspension test	Immobility period ↓	Yadav, Chatterjee, Majeed, and Kumar (2016)
Antistress activity	Aqueous extract of fruit	—	250 and 500 mg/kg	In vivo	In Sprague Dawley rats	Cold restraint stress	Stress-induced biochemical perturbations: plasma levels of glucose, triglycerides, cholesterol, total proteins and corticosterone ↓	Juvekar, Kulkarni, and Juvekar (2008)
	Aqueous extract	—	100 and 300 mg/kg	In vivo	Rat stress model	Urinary excretion as noninvasive biomarkers	All the urinary excretion vanillylmandelic acid (VMA), 5-hydroxyindoleacetic acid (5HIAA), and ascorbic acid were normalized	Srikanth and Venkatesh (2012)
	Alcohol extract	Piperine and piperlongumine	100, 200, and 300 mg per kg body weight	In vivo	Albino Wistar rats	Forced swim test	Stress-induced urinary biomarker VMA, 5HIAA, homo vanillic acid, and ascorbic acid levels were normalized in a dose-dependent manner	Kilari, Rao, Sreemanthula, and Kola (2015)
	Methanol extract of fruit and root		1–256 mg/kg/day	In vivo	Adult male Swiss albino mice	Foot shock stress triggered hyperthermia	Protection from foot shock stress triggered body weight losses and slight elevation in basal core temperatures	Yadav et al. (2016)
	Methanol extract of fruit	—	100, 250, and 500 mg/kg	In vivo	Mice and rats	Swimming endurance and immobilization stress models	Swimming performance time ↑ (dose-dependent), biochemical parameters-GSH and LPO levels ↓, and neurotransmitters-dopamine, nor adrenaline, and serotonin levels in the brain ↓	Nanjappaiah, Patil, Muchchandil, Chandrashekar, and Shivakumar (2017)
CNS depressant activity	Methanol extract of leaves	—	250 and 500 mg/kg	In vivo	Long-Evans rats	Open field and hole cross tests	Significant dose-dependent CNS depressant activity, locomotor activity ↓	Mamun et al. (2011)
Nootropic effect	Aqueous extract of fruit	—	250 and 500 mg/kg	In vivo	In Swiss albino mice	Passive avoidance model and elevated plus maze model	Step-down-latency ↑, transfer latency ↓	Juvekar et al. (2008)

TABLE 4 (Continued)

Activities	Plant parts/extracts	Effective phytocompounds	Tested concentrations	In vitro or in vivo experiment	Cell line/animal model	Experimental design	Results with mechanism of action	References
	Alcoholic extract	–	100, 200, and 300 mg per kg body weight	In vivo	Albino Wistar rats	Scopolamine-induced memory impairment in Y-maze apparatus model	Cognition, determined by working memory and locomotor activity ↑	Kilari et al. (2015)
Anticonvulsant activity	Aqueous extract of fruit	–	250 g and 500 mg/kg	In vivo	Seizures induced by PTZ, strychnine, and 4-aminopyridine in Swiss albino mice	–	GABA levels ↓	Juvekar et al. (2008)
Antiepileptic activity	Aqueous and ethanol extracts of fruits	–	100 μg/ml	In vivo	Audigenic stimulus-induced and MES-induced albino rats	–	Potential anticonvulsant activity by both extracts, maintained GABA level	Sharma, Singh, Gupta, and Sharma (2014)

Note: – indicates not mentioned in the retrieved literature.

et al., 2015). Ethanol extract of the fruits containing alkaloids exhibited a neuroprotective effect in 6-hydroxydopamine (6-OHDA)-induced PD rats when injected into the unilateral striatum. *Piper longum* extract administration decreased the time stayed on the rotary rod and significantly reduced the number of tyrosine hydroxylase (TH)-positive cells in substantia nigra and the density of TH-positive fibers in the striatum. The neuroprotective mechanism of the extract was attributed to its antioxidant activity (Zheng et al., 2014). In another experiment, improvement in behavioural dysfunction, as well as survival rate of tyrosine hydroxylase-immunoreactive (TH-ir) neurons in the SNpc and dopamine DA levels in the striatum, were observed following the administration of ethanol extract of the fruits in lipopolysaccharide (LPS)-induced Sprague–Dawley rats. Over-activated microglial cells were found to be suppressed, levels of inflammatory cytokines (TNF-α, IL-6, and IL-1β) were decreased and excessive production of ROS and NO were abolished following *P. longum* extract treatment (He et al., 2016). Alkaloids (piperine and piperlongumine) isolated from the extracts have exhibited protective effects in rotenone-induced PD in Wistar rat models. The observed protective effects involved improvement in rotenone-induced motor deficits, decrease in ROS production, stabilization in MMP, and inhibition of the opening of the mitochondrial permeability transition pore (mPTP). These alkaloids also abrogated apoptosis, stimulated autophagy, and mitigated neuronal injury suggesting their potential neuroprotective effect in the treatment of PD (Wang et al., 2016). Piperine isolated from the plant facilitated the protein phosphatase 2A (PP2A) and suppressed MTORC1 activity, thereby increasing autophagy in experimental PD models (Liu et al., 2016). Piperlongumine, another important alkaloid extracted from *P. longum* primarily restored autophagy via modulating BCL2 phosphorylation as it exhibited neuroprotection in the rotenone-induced PD mice model (Liu et al., 2018).

In the above-mentioned studies, the anti-PD properties of *P. longum* were mostly attributed to its ability to attenuate oxidative stress. *Piper longum* was mostly cited as a preventive anti-PD treatment owing to its multi-targeted efficacy against PD.

6.2.3 | Antidepressant activity

Monoamine oxidase (MAO) catalyses the oxidative deamination of monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine, and appears to play important roles in several psychiatric and neurological disorders. MAO-A inhibitors are useful in the therapy of mental disorders, mainly as antidepressants, whereas MAO-B inhibitors are expected to be useful in the therapy of PD and AD (Jegham & George, 1998; Shih, Chen, & Ridd, 1999). Piperine, obtained from *P. longum* fruit showed an inhibitory effect against MAO-A nd MAO-B and also reduced the immobility times in the tail suspension test similar to the antidepressant drug fluoxetine (Lee et al., 2005). The antidepressant activity of volatile oil from *P. longum* fruit, investigated by the force swim method in albino mice, was found to be more potent than fluoxetine (Khan, 2015). In another similar experiment, methylpiperate, guineensine, and piperlonguminine

were isolated; methylpiperate and guineensine showed significant MAO inhibitory activities; also methylpiperate selectively inhibited MAO-B over MAO-A (Lee et al., 2008). In a tail suspension test with adult male Swiss albino mice, methanol extracts of the fruits containing piperine and root containing piperlongumine, were found to shorten the immobility period following administration (Yadav et al., 2016).

6.2.4 | Antistress activity

Constant exposure to stresses in our daily life increases free radicals, and produces damage to neuronal receptors and a variety of tissues, which are hallmarks for a variety of diseases and disorders such as diabetes mellitus, hypertension, depression, anxiety, AD, immunosuppression, vascular disorders, cancer, male infertility, cognitive dysfunction, peptic ulcer, ulcerative colitis, ageing, arthritis, atherosclerosis, liver disease, and so on (McEwen, 2007; Uttara, Singh, Zamboni, & Mahajan, 2009). In a recent experiment, the stress resistance capacity of *P. longum* was investigated with the methanol extract of fruits containing piperine and piperlongumine in adult male Swiss albino mice against foot shock stress triggered alteration in body weights and core temperatures. The proper mechanism of action was not yet clear; however, the observations suggested that the extract might involve in desensitizing the stress-triggered hypersensitivity and might possess NSAID-like antinociceptive activity (Yadav et al., 2016). Juvekar et al. investigated the adaptogenic and antistress activities of the aqueous extract of *P. longum* fruit against chronic cold restraint stress and measured the biochemical perturbations in Sprague Dawley rats (Juvekar et al., 2008). To evaluate the antistress activity of daily treatment of *P. longum*, ethanol extract of fruits in rats subjected to forced swim stress, noninvasive urinary biomarkers such as vanillylmandellic acid, 5-hydroxyindoleacetic acid, homo vanillic acid, and ascorbic acid were estimated. The antistress activity of the extract was mostly attributed to its antioxidant property (Kilari et al., 2015). A similar kind of antistress activity was observed in the rat stress model where noninvasive biomarkers such as vanillylmandelic acid, 5-hydroxyindoleacetic acid and ascorbic acid in urinary excretions were normalized by the aqueous extracts of *P. longum* also indicating a possible correlation between urinary excretion of biogenic amine metabolites and stress (Srikanth & Venkatesh, 2012). The methanol extract of *P. longum* fruits was assessed for its antistress activity. Mice treated with the extracts showed dose-dependent increase in swimming performance time, fall in all the biochemical parameters, GSH and LPO levels, and neurotransmitters such as dopamine, noradrenaline, and serotonin levels in rat brain (Nanjappaiah et al., 2017).

The primary drawback in evaluating the antistress properties of the plant is the lack of validated and reproducible results in multiple models. Studies also didi not support the participation of the HPA axis and many biochemical modulations were nonspecific for stress responses. Validated pharmacological investigations are needed to clarify the underlying mechanism of adaptogenic properties of the plant and its components.

6.2.5 | Central nervous system depressant activity

Central nervous system (CNS) depressant activity of the methanol extract obtained from *P. longum* leaves was evaluated using open field and hole cross tests. The results showed that the plant extract had significant dose-dependent CNS depressant properties with reduced locomotor activity (Mamun et al., 2011). Further investigations are needed to understand the mechanism of its CNS depressant properties and proper dose forms. However, very little progress has been made in elucidating CNS activity in relation to the pharmacokinetics and the ability to cross the blood–brain barrier (BBB) of the *Piper* compounds in humans.

6.2.6 | Nootropic effect

The nootropic potential of the aqueous extract of *P. longum* fruit was assessed using a passive avoidance model and an elevated plus maze model in Swiss Albino mice (Juvekar et al., 2008). Another experiment also provided evidence in support of nootropic activity of the aqueous extract of *P. longum* fruit. The effect was estimated in terms of locomotor and working memory in rats in the Y-maze apparatus. The extract treatment prominently differentiated arm entries, duration of time spent in the novel arm, transfer latency for the novel arm, and spontaneous alteration behaviour of the rats compared to scopolamine treated groups (Kilari et al., 2015). Stress-induced memory loss was also found to be reversed by aqueous extract of *P. longum* by rectifying urinary excretion of biogenic amine metabolites in the rat model (Srikanth & Venkatesh, 2012).

Above mentioned results indicated an exciting opportunity to further exploit the pro-cognitive properties of *P. longum* as a memory booster and also in attenuating cognitive impairment. However, detailed studies are needed to explore the underlying signalling mechanisms and participation of the related receptors and neurotransmitters in elucidating the nootropic effects of *P. longum*.

6.2.7 | Anticonvulsant and antiepileptic activities

Epilepsy is a common neurological disorder closely associated with the generation of ROS and reactive nitrogen species which act on seizures via the inactivation of glutamine synthesis that results in the enhancement of L-glutamate levels in the brain. The altered concentration of CNS-neurotransmitters, decreased gamma amino butyric acid (GABA) transmission and voltage-gated channels are involved in epileptic seizures (Sharma, Singh, et al., 2014). *Piper longum* fruit extract exhibited protection against pentylenetetrazole (PTZ)-induced convulsions but failed to protect against strychnine and 4-aminopyridine-induced convulsions. The brain of mice treated with the extracts showed a diminution in GABA levels in comparison to the vehicle-treated mice clearly indicating the involvement of GABAergic mechanisms in the anticonvulsant activity (Juvekar et al., 2008). The potential anticonvulsant activity was also observed following the pre-

treatment with ethanol and aqueous extracts of *P. longum* fruit in audiogenic stimulus-induced seizures and maximal electroshock seizures (MES)-induced albino rats (Sharma, Kumar, et al., 2014; Sharma, Singh, et al., 2014).

The above-mentioned reports have provided the role of the GABAergic system following *P. longum* administration. In-depth studies on cellular and animal models are needed to explore the role of GABA receptors and its interaction with other receptors, neurotransmitters, and channels following *P. longum* treatment. Limited evidence indicated *P. longum*'s potential against acute seizures; however, its role against chronic seizures has not been elucidated yet. Besides, more studies regarding its toxicity and ability to cross BBB and further efforts to minimize its side effects on normal cognitive properties are needed to be performed.

6.3 | Antiinflammatory, analgesic, antiarthritic, and antiosteoporotic activities

Analgesic and antiinflammatory agents are clinically remarkable NSAID, continuous consumption of which may cause gastro intestinal ulcer, bleeding, and renal diseases due to nonselective inhibitors of both COX-1 and COX-2 (Kaushik, Rani, Kaushik, Sacher, & Yadav, 2012). Oral suspension of *P. longum* root aqueous extract was found to exhibit opioid-type analgesic effect and NSAID-type analgesia (Vedhanayaki, Shastri, & Kuruvilla, 2003). Mamun et al. found that the methanol extract of leaves reduced the number of writhes and licking time in Long-Evans rats by acetic acid induced writhing method and formalin test compared to reference drug indomethacin. The analgesic effect of the Piper extract was implicated in the presence of phytochemicals modulating prostaglandin pathways (Mamun et al., 2011). Methanol extract of the leaves was evaluated for carrageenan and dextran-induced paw oedema and cotton pellet-induced granuloma in Wistar rats. The results indicated that the carrageenan and dextran-induced inflammation and oedema were inhibited via the suppression of COX-2 and antihistamine or antiserotonin activities, respectively (Vaghasiya, Nair, & Chanda, 2007). A significant antiinflammatory effect was also observed in carrageenan-induced rat paw oedema in rats treated with *P. longum* fruit oil in comparison to the ibuprofen treatment (Kumar et al., 2009). Another experiment was conducted using two varieties of *P. longum* to evaluate their antiinflammatory effects in carrageenan-induced and formaldehyde-induced paw oedema in rats. Oral administration of aqueous extract showed antiinflammatory effect. Chhoti variety of the plant suppressed both acute and subacute types of inflammation, while the Badi variety only suppressed the acute phase. The observed effects were attributed to the inhibition of analgesic mediators, blocking their interactions with respective receptors and also by increasing cell membrane stability (Kumari, Ashok, Ravishankar, Pandya, & Acharya, 2012). Methanol extract of the fruit and piperlongumine were found to possess significant analgesic effects e in hot plate tests and in acetic acid-induced writhing tests in adult male Swiss albino mice (Yadav et al., 2016). Chauhan et al. found that supercritical fluid extract (SE) and isolated compounds possessed antiinflammatory effects stronger than indomethacin in RAW 264.7 murine macrophage cells by means of NO inhibition (Guo et al., 2019). *Piper longum* was found to be effective against inflammation in a rat model with cerebral ischemia. The antiinflammatory activity was exhibited by suppressing the expression or production of IL-1β, IL-6, and TNF-α. The treatment with the fraction also showed reducing oxygen-free radicals through increased SOD activity and decreased malonaldehyde levels (Wang et al., 2017). Antiinflammation was also observed in permanent focal cerebral ischemia injury in rats subjected to permanent middle cerebral artery occlusion (pMCAO). Dichloromethane fraction (DF) of *P. longum* alleviated neurological deficits and ischemia-induced cellular damage. Besides the levels of PSD-95 and syn-I proteins and p-CaMK II, CaM, and NR2B were also increased. Ultrahigh-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF/MS) revealed eight major constituents in the DF of which piperine was present in the largest amount. This work validated the use of *P. longum* as an ingredient in traditional Chinese Hui medicine in the treatment of stroke (Hua et al., 2019). One of the main constituents of *P. longum*, retrofractamide C was isolated and investigated for antiinflammatory effect on lipopolysaccharide (LPS)-induced J774A.1 cells and a xylene-induced mouse ear oedema model. The results showed decreased nitric oxide (NO) and prostaglandin E2 (PGE2) secretion and inducible cyclooxygenase 2 (COX2) and NO synthase (iNOS) protein expression. Interleukin-1β (IL-1β) and interleukin-6 (IL-6) expression were downregulated and phosphorylation of extracellular signal-regulated kinase (ERK) and nuclear factor kappa light chain enhancer of activated B cells (NF-κB) were inhibited. RAC treatment also alleviated oedema formation and inflammatory cell infiltration in the xylene-induced mouse ear oedema model (Lim et al., 2020).

Rheumatoid arthritis is a chronic inflammatory autoimmune disease of synovial joints characterized by severe bone destruction. Aqueous extract of the fruits of *P. longum* was evaluated for antiarthritic activity in Freund's adjuvant-induced arthritis containing 1 mg dry heat-killed *Mycobacterium tuberculosis* injection in Wistar rats. The aqueous extract significantly reduced the paw swelling suggesting *P. longum* extract as a potential antiarthritic agent mediated by its immuno-protective ability (Yende, Sannapuri, Vyawahare, & Harle, 2010). *Piper longum* fruit extract increased osteogenic differentiation of human Wharton's Jelly Mesenchymal Stem Cells (WJMSCs) coupled with a significant decline in apoptotic cells. In addition, the extract facilitated Ca^{2+} accumulation and matrix mineralization (Sanap, Joshi, Shah, Tillu, & Bhonde, 2021). *Piper longum* roots and fruits exhibited weak opioid but potent NSAID type of analgesic activity which to some extent supports its ethnopharmacological use as a febrifuge (Table 1). Methanol extract of fruit and piperlongumine compound demonstrated a significant analgesic effect.

Ethnopharmacological claim of using *P. longum* as a potent antiinflammatory and analgesic has not been fully validated for an underlying mode of action in cellular and animal models. In addition, no correlation has been reported on the impact of the plant extract and its metabolites on vanilloid receptors. Therefore, further studies are needed to elucidate the involvement and interaction of various

signalling pathways involved in *P. longum*-mediated antiinflammatory and analgesic properties. Antiarthritic properties are likely to be linked with immunomodulatory activities and impairment of histamine release from the mast cell. Therefore, the plant extracts and the fractions deserve in-depth investigations to find out the bioactive compounds responsible for its antiarthritic potential. However, limited biochemical analysis and toxicological information as well as unestablished dose-effect relationships restrict the applicability of the plant extracts against arthritis. Therefore, more insights into the antiarthritis effects are needed to elucidate the involvement of signalling pathways and their interaction with *P. longum* preparations.

In ethnomedicine, the plant is very commonly used as a febrifuge. Therefore, the plant extracts and its compounds may further be tested for potential bioactive molecules active against fever and pain. Osteoporosis, a common disease in senior individuals, is indicated by low bone mass with an enhanced risk for bone fracturing due to minor trauma. The surgeries and medication require a long recovery period and are very expensive. *Piper longum* exhibited promising antiosteoclastic activity without exhibiting any toxic effects. Therefore, osteogenic potential of the plant can be clinically translated into antiosteoporotic agent development. Antiinflammatory, analgesic, and antiarthritic activities of *P. longum* are mentioned in Table 5.

6.4 | Antihyperglycaemic activity

Diabetes mellitus is one of the significant metabolic syndromes that accounts for the highest morbidity and mortality worldwide, characterized by carbohydrate, lipid, and protein metabolism abnormalities due to incomplete or relative insufficiency of insulin secretion from pancreatic β-cells and/or imbalance in insulin action (Unger & Foster, 1998). Antihyperglycaemic activity of *P. longum* was observed in streptozotocin-induced albino Wistar rats. Root extracts of indifferent solvents (hexane, ethyl acetate, methanol, and aqueous) were administered for short and long-term studies. The result showed a significant antihyperglycaemic effect of the methanol and aqueous extracts. In addition, the aqueous extract showed a superior antidiabetic effect with a significant decrease in FBG levels with the corrections of diabetic dyslipidaemia. The plant extracts reduced the marker protein HbA1c for glycation in diabetes mellitus and probably enhanced glucose utilization to decrease the blood glucose level (Nabi et al., 2013). In another experiment, essential oils from the root were administered in streptozotocin- and nicotinamide-induced type 2 diabetes mellitus in albino Wistar rats. The essential oil significantly reduced the blood glucose level, increased body weight, the levels of liver glycogen content and plasma insulin, and decreased the level of glycosylated haemoglobin. Antihyperglycemic properties of the essential oil were implicated in the reduction of α-glucoside and aldose reductase enzyme activities (Kumar, Sharma, & Vasudeva, 2013). Alloxan monohydrate-induced diabetic Wistar rats treated with ethanol extract of the root exhibited improved blood glucose content, lipid profile, glycogen content (liver and muscles), serum insulin content, glucose 6-phosphatase, and hexokinase in the liver (Chaurasia & Das, 2013). A similar experiment was performed with ethanol extract of the fruits which corrected the metabolic alterations by the activities of several carbohydrates metabolizing enzymes (hexokinase, glucose-6-phosphatase, glucose-6-phosphate dehydrogenase, fructose-1.6-bisphosphatase, and glycogen phosphorylase) in alloxan-induced diabetic rats (Shanmugam Manoharan, Vasudevan, & Balakrishnan, 2007). In silico approach with molecular docking technique confirmed a few important phytochemicals namely piperine, piperlongumine, piperlonguminine, and retrofractamide A acting as inhibitors for dipeptidyl peptidase-4, GKRP, glutamine-fructose-6-phosphate transaminase 1, 11β-hydroxysteroid dehydrogenase type 1, and protein tyrosine phosphatase 1B, which are involved in the glucose digestion and increment in insulin affectability and thus proving the efficacy of *P. longum* against diabetes (Thakuria, Laskar, & Adhikari, 2020).

P. longum attenuated a number of diabetes-related primary symptoms including enhanced blood glucose level, oxidative stress, reduction of antioxidant marker enzymes, and total soluble protein, validating its popular traditional use as an effective antihyperglycaemic agent. Ayurveda has also recognized *P. longum* against diabetes. The above-cited reports also present some pre-clinical evidence in the treatment of diabetes and allied complications.

6.5 | Antihyperlipidaemic activity

Han et al. synthesized a novel starch piperinic ester with hyperlipidaemic activity with the isolated piperine from the seed extract of *P. longum*; hydrolysed it to piperic acid; then activated the piperic acid by reacting with carbonyldiimidazole (CDI) in dimethyl sulfoxide (DMSO), and finally reacted with water-soluble starch to obtain piperinic ester. Hyperlipidaemia was introduced in Wistar rats by feeding them with cholesterol-rich diet. Piperinic ester was investigated with different pharmacological tests and the results exhibited reduced serum total cholesterol (TC), total triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein (VLDL), and increased high-density lipoprotein cholesterol (HDL-C) indicating it as a novel antihyperlipidaemic pro-drug candidate (Han et al., 2008). In vivo hyperglycaemic activity of *P. longum* was assessed with the obtained piperlonguminine, piperine, and pipernonaline from the ethanol extract and fractions of fruit and on hyperlipidemic Wistar rats fed with a cholesterol-rich diet. The result showed lowered serum total cholesterol and slightly decreased serum triglyceride when compared to that of the commercial antihyperlipidaemic drug simvastatin (Jin et al., 2009). Another experiment was conducted where antihyperlipidaemic activity of *P. longum* was measured in streptozotocin and nicotinamide-induced diabetic Wistar mice. Administration of essential oil from *P. longum* fruit containing piperine was found to increase the body weight, HDL and to decrease triglyceride, and total plasma cholesterol in the animals. The antihyperlipidaemic activity of the essential oil was possibly attributed to the inhibition of pancreatic lipase enzymes (Kumar et al., 2013). The antihyperlipidaemic activity of the aqueous extract of *P. longum* roots was also evaluated in the

TABLE 5 Antiinflammatory, analgesic, and antiarthritic activities of *P. longum*

Effects	Parts/extracts	Effective phytocompound	Tested concentrations	In vitro or in vivo experiments	Experimental design	Model	Results/mechanism of action	References
Antiinflammatory and analgesic activities	Aqueous root suspension	—	200, 400 and 800 mg/kg	In vivo	Acetic acid writhing method	Mice	NSAID type of analgesia ↑ (by dose dependant manner)	Vedhanayaki et al. (2003)
	Methanol extract of leaves	—	300 mg/kg	In vivo	Carrageenan and dextran-induced paw oedema and cotton pallet-induced granuloma	Wistar rats	Paw oedema ↓ (39.81% and 67.51%) in carrageenan and dextran model, no effect in cotton pallet model	Vaghasiya et al. (2007)
	Essential oil from fruit	—	0.5 ml/kg and 1 ml/kg	In vivo	Carrageenan-induced rat paw oedema	Rats	Significant antiinflammatory activity compared to ibuprofen	Kumar et al. (2009)
	Methanol extract of leaves	—	250 and 500 mg/kg body weight	In vivo	Acetic acid-induced writhing method and formalin test	Long-Evans rats	Number of writhes (57.58%) and licking time (58.8%) ↓	Mamun et al. (2011)
	Aqueous extract of two varieties (Chhoti pippali and Badi pippali)	—	200 mg/kg	In vivo	Carrageenan-induced rat paw oedema and formaldehyde-induced paw oedema	Albino Wistar rats	Both acute and subacute inflammation ↓ (by Chhoti variety), only acute phase compared to diclofenac sodium ↓ (by Badi variety)	Kumari et al. (2012)
	Methanol extract of fruit	Piperlongumine	5 mg/kg	In vivo	Hot plate test and in acetic acid-induced writhing tests	Adult male Swiss albino mice	Significant analgesic effect compared to standard drugs aspirin and doxycycline	Yadav et al. (2016)
	Dichloromethane fraction of fruit	—	200 mg/kg	In vivo	Biochemical analysis, ELIZA	Rat model with cerebral ischemia	IL-1β, IL-6, and TNF-α ↓; oxygen-free radicals ↓; SOD activity ↑, MDA level ↓	Wang et al. (2017)
	Ethanol reflux, ultrasonic and supercritical fluid extraction	—	0.5 mg/100 ml and 1 mg/100 ml	In vivo	Inhibition effect of NO by Griess assay	RAW 264.7 murine macrophage cell	Antiinflammatory effect stronger than indomethacin (supercritical fluid extract and isolated compounds)	Guo et al. (2019)

(Continues)

TABLE 5 (Continued)

Effects	Parts/extracts	Effective phytocompound	Tested concentrations	In vitro or in vivo experiments	Experimental design	Model	Results/mechanism of action	References
	Dichloromethane fraction of fruit	—	200 mg/kg	In vivo	Histopathology and	Sprague-Dawleyrat with focal cerebral ischemia	Neurological deficits ↓, cellular damage↓; PSD-95 and syn-I proteins ↑; p-CaMK II, CaM, and NR2B ↑	Hua et al. (2019)
	Fruit extract	Retrofractamide C	1, 3 and 10 μM	In vivo	MTT assay, ELIZA, RT PCR, immunoblot	Lipopolysaccharide (LPS)-induced J774A.1 cells and a xylene-induced mouse ear oedema model	NO and PGE2 secretion, COX2, and NO synthase, iNOS protein expression ↓; IL-1β and IL-6 expression↓, phosphorylation of ERK and NF-κB ↓, oedema formation and inflammatory cell infiltration ↓	Lim et al. (2020)
Anti-arthritic activity	Aqueous extract of fruits	—	200 and 400 mg/kg	In vivo	Arthritis induced by Freund's adjuvant containing 1.0 mg dry heat-killed *Mycobacterium tuberculosis* injection	Wistar rats	Paw swelling ↓	Yende et al. (2010)
Antiosteoporotic activity	Fruit extract	—	5 and 10–100 μg/ml	In vitro	MTT assay and cell cycle analysis	Human Wharton's jelly mesenchymal stem cells (WJMSCs)	Osteogenic differentiation of WJMSCs ↑	Sanap et al. (2021)

streptozotocin-induced diabetic albino Wistar rats that resulted in decreased TC, LDL, VLDL, triacylglycerol, cholesterol, and increased HDL levels besides potentiating protection against atherogenicity (Nabi et al., 2013). Mungunnaran et al., isolated piperine from *P. longum* and synthesized a derivative named piperlonguminine acid, which was administered to high-fat diet-fed hyperlipidemic rats. A significant decrease in the levels of serum TC, TG, and LDL-C was observed while, HDL-C level was increased (Mungunnaran, Gereltu, & Bayarmaa, 2018).

Investigations revealed that diabetic dyslipidemia was corrected and lipid profile was improved in the experimental rats following the administration of the *P. longum*. However, this primary data necessitates elaborate clinical studies and dose-optimization to prove the efficacy of the plant in the dietary management of diabetic as well as hyperlipidaemic patients. Antihyperglycaemic and antihyperlipidaemic activities of *P. longum* are presented in Table 6.

6.6 | Antioxidant activity

Ethanol extract of the *P. longum* fruits when administered in monosodium glutamate (MSG)-induced oxidative stress in rats, offered protection to the liver and the kidney from oxidative stress by reducing lipid peroxidation, aspartate aminotransferase (AST) activity, TG, and TC and by increasing GSH level (Thomas, Sujatha, & George, 2009). Different solvent (hexane, ethyl acetate, methanol, and 70% methanol–water) extracts of the fruit and isolated apigenin 7, 4′-dimethyl ether (ADE) were used to assess the antioxidant property by in vitro total reducing power (TRP) assay, 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, hydroxyl radical scavenging assay and SOD activity in HepG2 cell line and inhibition of human LDL oxidation in vitro (Krishna, Joy, & Sundaresan, 2015). Hydro-alcoholic extract and ethyl acetate fractions exhibited a free radical scavenging effect in the DPPH assay (Chaudhary et al., 2013). In another experiment, the antioxidant activity of the ethanol extract of the seeds of *P. longum* was investigated via in vitro DPPH assay and superoxide, NO, and hydroxyl radical scavenging activities (Ramesh, Hari, Pandian, & Arumugam, 2011). In addition, the antioxidant activity of different solvent extracts of the fruits was evaluated using a ferric reducing antioxidant power (FRAP) assay. The aqueous extract exerted the highest activity followed by methanol and ethyl acetate extracts in terms of free radical scavenging properties (Sawhney et al., 2011). Jagdale et al. used petroleum ether extract of the roots for in vivo DPPH scavenging, lipid peroxidase, and GSH assays in myocardial ischemic Wistar rats and the result showed 71.13% inhibition of free radical, decreased lipid peroxidation, and maintained GSH level indicating *P. longum* as a potent natural antioxidant agent (Jagdale, Kuchekar, Chabukswar, Lokhande, & Raut, 2009). Methanol extract of the leaves was also found to exhibit superoxide, hydroxyl, lipid peroxide, and DPPH radical scavenging activity (Kumar & Prathyusha, 2019). The antioxidant activity of ethanol and water extracts of *P. longum* was evaluated by DPPH free radical scavenging assay (Aung et al., 2020).

In some of the above-mentioned studies, the plant extract exhibited superior antioxidant activities compared to the isolated compounds. This may be implicated in the synergistic activities often demonstrated by the crude extracts and fractions showing higher efficacy than the pure compounds. In addition, DPPH and other free radical scavenging assays do not present a pharmacological basis limiting their clinical applications. Besides, disease pathogenesis of a number of ailments involves the generation of ROS which are subsequently attenuated using antioxidants such as plant extracts and compounds. Therefore, novel strategies dealing with the in vivo analysis of antioxidant properties might be utilized to assess the antioxidant capacity of plant extracts with possible therapeutic applications.

6.7 | Hepatoprotective activity

Chronic liver damage causes liver fibrosis which is a common cause of death in human characterized by excessive scarring, enhanced production and deposition of collagen due to decreased collagenolytic activity that result in cirrhosis, liver failure, and hypertension and may require liver transplantation (Latief & Ahmad, 2018;). Ethanol extract of the *P. longum* fruits was chosen to evaluate its antifibrotic effect in Wistar rats following liver fibrosis induced by carbon tetrachloride (CCl_4) with liquid paraffin (1:1) treatment. The study revealed that the extract promisingly inhibited liver fibrosis by reducing the hydroxyproline and serum enzymes and also by decreasing liver weight (Christina et al., 2006). Gurumurthy et al. studied the hepatoprotective activity of *P. longum* aqueous extract against hepatotoxicity induced by antitubercular drugs (isoniazid, rifampicin, and pyrazinamide) in Swiss albino mice. Administration of aqueous extract of *P. longum* increased the reduced GSH levels and decreased lipid peroxidation (Gurumurthy, Vijayalatha, Sumathy, Asokan, & Naseema, 2012). Another experiment was performed where hepatic damage was induced in Swiss albino mice by treating with CCl_4 with olive oil (1:1). Ethanol extract of the fruits and its five fractions (crude, petroleum ether, ethyl acetate, butanol, and butanone) were screened for hepatoprotective activity; significant activity was observed for ethanol extract and butanol fraction which reduced the enzymes serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) (Jalalpure, Patil, Prakash, Hemalata, & Manvi, 2003). In addition, *P. longum* fruit extract mixed with milk protected rats against CCl_4-induced liver damage by decreasing the levels of serum enzymes and by reducing the total bilirubin and direct bilirubin (Patel, 2009). Ethanol extract of the seeds and a biherbal extract prepared by mixing the plant with *Melia azedarach* leaves extract were also found to reduce serum marked enzyme level and the total protein, bilirubin, triglyceride, and urea were also restored, singly or by mixing both. A similar experiment was conducted by Samudram et al., which showed that the same biherbal extract maintained the levels of serum marker enzymes such as SGOT, SGPT, alkaline phosphatase (ALP), acid phosphatase (ACP), and lactate dehydrogenase (LDH) and attenuated liver toxicity induced by CCl_4 (Samudram, Vasuki, Rajeshwari, Geetha, & Moorthi, 2009). Another

TABLE 6 Antihyperglycaemic and antihyperlipidaemic activities of *P. longum*

Effects	Plant parts/extracts	Effective concentration	Tested concentrations	In vivo and in vitro study	Model	Results	References
Antihyperglycaemic activity	Root hexane, ethyl acetate, methanol, and aqueous extracts	—	200 mg/kg	In vivo	Streptozotocin-induced albino Wistar rats	Significant antihyperglycaemic effect with the corrections of diabetic dyslipidaemia, FBG ↓ (30% and 75% by methanol and aqueous extracts respectively)	Nabi et al. (2013)
	Essential oil from fruits	—	100 and 200 mg/kg	In vivo	Streptozotocin and nicotinamide (110 mg/kg) induced type 2 diabetes mellitus in albino Wistar rats	Blood glucose level ↓, body weight ↑, liver glycogen content, plasma insulin and glycosylated haemoglobin ↓	Kumar et al. (2013)
	Ethanol extract of roots	—	150 mg/kg	In vivo	Alloxan monohydrate induced diabetes in rats	Improvement in blood glucose content, lipid profile, glycogen content (liver and muscles), serum insulin content, glucose 6-phosphatase, and hexokinase enzymes in the liver	Chaurasia and Das (2013)
	Ethanol extract of fruits	—	150 mg/kg	In vivo	Alloxan monohydrate-induced diabetes in Wistar rats	Blood glucose level ↓, corrected alteration of carbohydrate metabolizing enzymes (hexokinase, glucose-6-phosphatase, glucose-6-phosphate dehydrogenase, fructose 1.6-bisphosphatase, and glycogen phosphorylase)	Shanmugam Manoharan et al. (2007)
		Piperine, piperlongumine, piperlonguminine, and retrofractamide A	—		In silico model with molecular docking technique	Dipeptidyl peptidase-4, GKRP, glutamine-fructose-6-phosphate transaminase 1, 11β-hydroxysteroid dehydrogenase type 1, and protein tyrosine phosphatase 1B ↓	Thakuria et al. (2020)
Antihyperlipidaemic activity	Ethanol extract of fruits	Piperine, piperic acid, piperinic ester	4 ml/kg	In vivo	Wistar rats fed with cholesterol-rich diet	Serum TC, TG, LDL-C and VLDL ↓; HDL-C ↑	Han et al. (2008)

TABLE 6 (Continued)

Effects	Plant parts/extracts	Effective concentration	Tested concentrations	In vivo and in vitro study	Model	Results	References
	Ethanol extract and fractions of fruit	Piperlonguminine, piperine and pipernonaline	20 mg/kg BW, 5.6 mg/kg	In vivo	Wistar rats fed with cholesterol-rich diet	The serum TC and serum TG ↓	Jin et al. (2009)
	Essential oil from fruits	Piperine	100 and 200 mg/kg	In vivo	Streptozocin and nicotinamide administered Wistar mice	Body weight ↑, HDL and glycosylated haemoglobin, TG, and total plasma cholesterol ↓	Kumar et al. (2013)
	Root aqueous extract	–	200 mg/kg	In vivo	Streptozotocin induced albino Wistar rats	TC, LDL, VLDL and triacylglycerol, cholesterol ↓; HDL and protected against atherogenicity ↑	Nabi et al. (2013)
	Piperlonguminine acid derivative from isolated piperine		10 mg/kg	In vivo	High-fat diet fed hyper-lipidemic rats	TC, TG, and LDL-C levels ↓; HDL-C level ↑	Mungunnaran et al. (2018)

biherbal ethanol extract prepared with the fruits of *P. longum* and the leaves of *Abutilon indicum* (1:3) was found to inhibit liver damage induced by CCl_4 in olive oil (1:1 v/v, i.p) in adult Charles foster rats by reducing the rise in the liver injury markers such as SGOT, SGPT, total bilirubin, direct bilirubin, and ALP when administered prior to liver injury (Sharma & Sahu, 2016). Sharma et al. observed the biochemical efficacy of *P. longum* fruit against the aluminium chloride ($AlCl_3$)-induced hepatotoxicity in Wistar rats. The aqueous extract of the fruits significantly attenuated the hepatic toxicity by altering SGOT, SGPT, and ALP activities, as well as the creatinine and bilirubin content indicating *P. longum* exerts a protective effect against metal induced hepatotoxicity (Sharma, Kumar, et al., 2014). Ethanol (40%)-induced hepatotoxicity in Wistar rats was found to be cured by administration of methanol extract with the reduction in elevated serum hepatic biomarkers (AST, ALP, ALT, and TB), physical parameters (liver weight and volume), and antioxidant enzyme (SOD, CAT, and GPx) (Kumar & Prathyusha, 2019).

Some studies indicated the possible involvement of the *P. longum* flavonoids in protecting the liver from different ailments. Most of the studies indicated the modulation of hepatic biomarkers flowing through the administration of the plant extracts. However, in a few studies, a single acute dose was preferred whereas it was suggested otherwise in another record. Therefore, many such investigations appeared to be preliminary in nature with further need to elucidate the optimum dose as well as the underlying molecular mechanism of hepatoprotection.

6.8 | Antiulcer activity

Piper longum was studied for its antiulcerogenic property and its mechanism for offering antiulcer effect following gastric ulcer induced by cold restraint stress, aspirin, and pylorus ligation in CF strain rats. Significant antiulcerogenic effect of the aqueous decoction of fruits was observed due to modulation of mucin secretion and decreased cell shedding, and offensive acid and pepsin secretion (Agrawal, Rao, Sairam, Joshi, & Goel, 2000). Yadav et al. showed that occasional exposure to foot shock can form gastric ulcers in rats which can be protected by 90% by the administration of *P. longum* extract. However, the experiment did not elucidate the ulcer-related biochemical information and underlying mechanisms of action (Yadav, Chatterjee, Majeed, & Kumar, 2015). However, the above-mentioned studies present a few shortcomings such as a lack of investigations on cell proliferation, biochemical markers as well as mucosal blood flow.

A peptic ulcer is considered one of the very common diseases affecting urban people in India. *Piper longum* exhibited significant prophylactic and curative effects against an ulcer in a rat model. *Piper longum* demonstrated significant prophylactic and curative properties against an ulcer in a rat model. Since the plant is a popular edible species, its ulcer-preventive and muco-protective properties can be exploited to manage gastric ulcers in urban populations. Antioxidant, hepato-protective, and antiulcer activities of *P. longum* are presented in Table 7.

TABLE 7 Antioxidant, hepatoprotective, and antiulcer activities of *P. longum*

Effects	Extracts	Tested concentrations	In vitro/in vivo experiment	Model	Results	References
Antioxidant activity	Ethanol extract of fruits	300 mg/kg b.w.	In vivo	Biochemical analysis in MSG-induced oxidative stress in rats	Provided protection to the liver and kidney from oxidative stress lipid peroxidation, AST activity, TG, TC ↓, and GSH level ↑	Thomas et al. (2009)
	Fruits extracts using hexane, ethyl acetate, methanol, 70% methanol–water, and isolated apigenin 7, 4′-dimethyl ether (ADE)	0.1–10 μg/ml	In vitro	TRP assay, DHPP assay, hydroxyl radical scavenging assay, SOD activity in HepG2 cell line, inhibition of human LDL oxidation in vitro	Highest antioxidant activity by ethyl acetate extract in terms of TRP (196.03 μg/mg GAE), free radical scavenging (IC_{50}: 173.09 μg/ml), hydroxyl radical scavenging (IC_{50}: 20.42 μg/ml), LDL oxidation ↓ (IC_{50}: 51.99 μg/ml), SOD activity ↑ (25.3%)	Krishna et al. (2015)
	Hydroalcoholic extract and ethyl acetate fractions	50–500 μg/ml	In vitro	DPPH assay	Radical scavenging ↑ (IC_{5o} values of 193.12 μg/ml and 247.78 μg/ml respectively for extract and fraction)	Chaudhary et al. (2013)
	Ethanol extract of seeds	100–1,000 μg/ml	In vitro	DPPH assay, super oxide, nitric oxide, hydroxyl radical scavenging activity	Antioxidant activity ↑	Ramesh et al. (2011)
	Aqueous, methanol, and ethyl acetate extracts of fruits	10, 50, and 100 μg/ml	In vitro	FRAP assay	Highest antioxidant activity by aqueous extract followed by methanol and ethyl acetate extracts, radical scavenging	Sawhney et al. (2011)
	Ethanol and watery extracts of fruits	6.25–200 μg/ml	In vitro	DPPH scavenging assay	IC_{50} values of ethanol and watery extracts: 43.52 and 64.28 μg/ml, respectively	Aung et al. (2020)
	Petroleum ether extract of the root	50 mg/ml	In vivo	In vivo DPPH scavenging assay, lipid peroxidase, and GSH assay in myocardial ischemic Wistar rats	Of free radical ↓ (71.13%), lipid peroxidation ↓, GSH level maintained	Jagdale et al. (2009)
	Methanol extract	100, 200, and 400 mg/kg body weight	In vitro	Superoxide, hydroxyl, lipid peroxide, and DPPH radical scavenging activities	IC_{50} values for superoxide, hydroxyl, lipid peroxide, and DPPH radical scavenging activity were 265.79, 430.89, 608.44, and 338.59 μg/ml respectively	Kumar and Prathyusha (2019)

TABLE 7 (Continued)

Effects	Extracts	Tested concentrations	In vitro/in vivo experiment	Model	Results	References
Hepato-protective activity	Ethanol extract of fruits	50 and 100 mg/kg	In vivo	Liver fibrosis induced in Wistar rats treated with CCl_4 with liquid paraffin (1:1)	Hydroxyproline, serum enzymes, and liver weight ↓	Christina et al. (2006)
	Aqueous extract	0.5 g/kg body weight	In vivo	Antitubercular drugs (isoniazid, rifampicin, and pyrazinamide) induced Swiss albino mice	Reduced GSH level ↑ and lipid peroxidation ↓	Gurumurthy et al. (2012)
	Ethanol extract and five fractions (crude, petroleum ether, ethyl acetate, butanol, and butanone) of fruits	300 mg/kg	In vivo	Hepatic damage induced in Swiss albino mice treated with CCl_4 with olive oil (1:1)	Serum enzyme SGOT and SGPT ↓	Jalalpure et al. (2003)
	Fruit and root extracts in milk	200 mg/kg	In vivo	Wistar rats treated with CCl_4 with olive oil (1:1)	Levels of serum enzymes, total bilirubin, and direct bilirubin ↓	Patel (2009)
	Ethanol extract of seeds and bi-herbal extract mixed with *Melia azedarach* leaves extract	50 mg/kg	In vivo	Wistar rats treated with CCl_4	Serum marked enzyme level ↓; total protein, bilirubin, TG, and urea were restored	Rajeswary, Vasuki, Samudram, and Geetha (2011),
	Biherbal extract (seed extract mixed with *Melia azedarach* leaves extract)	50 mg/kg	In vivo	Wistar rats treated with CCl_4	Maintenance in the levels of serum marker enzymes such as SGOT, SGPT, ALP, ACP, and LDH	Samudram et al. (2009)
	Fruit extract mixed with *Abutilon indicum* leaves extract	100, 200, and 400 mg/kg p.o	In vivo	Charles foster rats treated with CCl_4 with olive oil (1:1)	Liver injury markers such as SGOT, SGPT, total bilirubin, direct bilirubin, and ALP ↓	Sharma and Sahu (2016)
	Fruit aqueous extract	50 mg/kg	In vivo	$AlCl_3$-induced Wistar rats	Altered SGOT, SGPT, ALP, also creatinine and bilirubin content	Sharma, Kumar, et al. (2014); Sharma, Singh, et al. (2014)
	Methanol extract	100, 200, 400 mg/kg body weight	In vivo	40% ethanol-induced hepatotoxicity in Wistar rats	Serum hepatic biomarkers AST, ALP, ALT, TB, liver weight, and volume↑, antioxidant enzyme SOD, CAT, and GPx ↓	Kumar and Prathyusha (2019)
Antiulcer activity	Water decoction of fruits	50 mg/kg		Cold restraint stress, aspirin, pylorus ligation induced CF strain rats	Augmentation of mucin secretion, cell shedding, offensive acid ↓, pepsin secretion ↑	Agrawal et al. (2000)

6.9 | Biocidal activities

6.9.1 | Antibacterial activity

A number of studies have reported the antibacterial effects of *P. longum*. Earlier, the antibacterial effect of the seed oil was recorded against three bacterial strains namely *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (Arambewela, Perera, & Wijesundera, 1999). Three isolates such as piperlonguminine, piperine, and pellitorine from a dichloromethane methanol extract of the fruits showed potent activity against the Gram-positive bacteria and moderate activity against the Gram-negative bacteria. Each isolate was found to be highly active against at least one particular species of bacteria; piperlonguminine against *Bacillus subtilis*, piperine against *S. aureus*, and pellitorine against *Bacillus sphaericus* (Srinivasa Reddy, Jamil, Madhusudhan, Anjani, & Das, 2001). Different solvent extracts of *P. longum* fruits were used by Khan and Siddiqui to evaluate their antibacterial property. They observed promising antibacterial activity of the extracts against *Staphylococcus albus*, *Bacillus megaterium*, *Salmonella typhi*, *P. aeruginosa*, and *E. coli* (Khan & Siddiqui, 2007). Antibacterial activities of various solvent extracts of fruits were determined against a wide range of pathogenic bacteria. The crude extracts showed mild to moderate activities, while the ethyl acetate extracts showed relatively superior antimicrobial effects against most of the bacteria but the petroleum ether extracts were found to be inactive in this regard (Ali et al., 2007). Another experiment was performed where the dry roots were extracted with n-hexane and different compounds (piperine, piperlongumine, piperlonguminine, piplartine, etc.) were isolated. All the compounds showed promising inhibition against *E. coli*, *P. aeruginosa*, *B. cereus*, *S. typhi*, *Serratia marcescens*, *S. aureus*, *Shigella dysenteriae*, *Klebsiella pneumoniae*, and so on while the n-hexane extracts showed inhibition zone against only the Gram-positive bacteria (Lokhande et al., 2007). Another experiment revealed the potential of the methanol, ethanol, and acetone fruit extracts against the tested bacteria *Streptococcus mutans* and *S. aureus* (Aneja, Joshi, Sharma, & Aneja, 2010). The methanol extract showed an inhibitory effect against *B. subtilis*, *Pseudomonas fluoresces*, *E. coli*, and *S. typhi* (Reshmi, Sathya, & Devi, 2010). Root extract and isolated compound piperlongumine were assessed for their antibacterial activity against 18 clinically isolated strains, including identified strains such as *P. aeruginosa*, *K. pneumoniae*, and *S. aureus*, using the agar-well diffusion method. All extracts showed concentration-dependent inhibition against all the clinical strains with more pronounced activity against *K. pneumoniae* (Naika, Prasanna, & Ganapathy, 2010). Agar well diffusion method and broth dilution MIC tests with ethyl acetate, methanol, and water extracts of the fruits were employed against *S. aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *K. pneumoniae*. The extracts displayed high to moderate inhibition zones against the bacteria *S. aureus* (Sawhney et al., 2011). In addition, the fruit extracts in polar and nonpolar solvents inhibited the human pathogenic bacteria, determined by the agar-well diffusion method and MIC assay. The ethyl acetate extract was found to be the most effective against the selected pathogenic bacteria in comparison with gentamicin as control (Chauhan, Uniyal, Chauhan, Singh, & Kumar, 2019).

Antibacterial properties of *P. longum* were mostly attributed to the alkaloids and essential oil present in the extracts. However, such conventional antibacterial assays involving agar well or diffusion methods have limited applications. In addition, time and dose dependence, toxicity, mechanism of action, and so on are also needed to be established for proper understanding of the antimicrobial properties presented by *P. longum*.

6.9.2 | Antifungal activity

The fungicidal activity of *P. longum* fruit extract, its hexane fraction, and isolated compound pipernonaline was investigated towards six phytopathogenic fungi namely *Pyricularia oryzae*, *Rhizoctonia solani*, *Botrytis cinerea*, *Phytophthora infestans*, *Puccinia recondita*, and *Erysiphe graminis*, and the results were compared with the synthetic fungicideschlorothalonil, dichlofluanid, and mancozeb. The hexane extract showed fungicidal activities against *P. oryzae*, *B. cinerea*, *P. infestans*, and *P. recondita* while pipernonaline showed potent fungicidal activity against *P. recondita* (Lee et al., 2001). Khan and Siddiqui found that chloroform, ethyl acetate, acetone, and ethanol extract showed antifungal activity only against *Aspergillus niger* among the six tested fungi (Khan & Siddiqui, 2007). Various extracts of *P. longum* roots were evaluated for their antifungal activity against *Penecillum* sp., *A. niger*, *Aspergillus fumigatus*, *Mucor* sp., *Fusarium* sp., and *Candida albicans* (Ali et al., 2007). In another experiment, the methanol, ethanol, and acetone fruit extracts showed almost equal inhibition zones for both fungi *C. albicans and Saccharomyces cerevisiae* (Aneja et al., 2010).

The above-mentioned studies indicated the possible application of *P. longum* against keratinophilic fungi and also against multidrug resistance in relation to fungal infections. In addition, studies on animal models are needed to evaluate its toxicity and safety as promising antifungal agents. Synthetic fungicides are known to produce unwanted adverse effects such as teratogenicity, carcinogenicity, and acute toxicity and need a long degradation time. Natural products used as fungicides are in general safer than synthetic since they show shorter environmental half-life, reduced or no toxicity, and adverse effects on humans. Therefore, the use of *P. longum* and its phytochemicals as a natural fungicide should be tested at the clinical level given its wide use in traditional medicine especially against the fungi causing dermatological infections.

6.9.3 | Antiparasitic activity

Piper longum fruit extracts were evaluated for their efficacy against experimental infection of *Giardia lamblia* in mice. Aqueous and ethanol extracts showed 100% giardicidal activity in vitro. *Piper longum* possessed immuno-stimulatory activity, which was evident from the standard test parameters such as haemagglutination assay (HA), plaque-

forming cell (PFC) counts, macrophage migration index (MMI), and phagocytic index (PI) (Tripathi, Gupta, Lakshmi, Saxena, & Agrawal, 1999). Pippali rasayana, an Ayurvedic herbal medicine, prepared from *P. longum* and *Butea monosperma*, was tested for its antigiardial and immuno-stimulatory activities in mice infected with *Giardia lamblia* trophozoites. Although the rasayana exhibited no killing of trophozoites in vitro, but produced up to 98% recovery from the giardial infection by activation of macrophages and phagocytic activity with an enhancement in host resistance (Agarwal et al., 1994). Sawangjaroen et al., in their study, showed that *P. longum* methanol extract affected 50% of *Blastocystis hominis* and killed it by 50% (Sawangjaroen et al., 2005). Antileishmanial property of *P. longum* was evaluated in an experiment that revealed that the plant extract can eliminate *Leishmania donovani* promastigotes (Singh et al., 2011). In another investigation, seven known compounds including piperlongumide were isolated from the n-hexane extract which showed leishmanicidal activity against the promastigotes and axenic amastigotes of *L. donovani* and piperlongumide was found to be the most potent against the promastigotes and axenic amastigotes (Ghosal, Deb, Mishra, & Vishwakarma, 2012).

6.9.4 | Scolicidal activity

Methanolic extract of *P. longum* exhibited antiparasitic activity against protoscolices of hydatid cysts of *Echinococcus granulosus*. This is the pioneer demonstration of scolicidal activity of *P. longum* (Cheraghipour et al., 2021).

6.9.5 | Anthelmintic and insecticidal properties

The anthelmintic potential of *P. longum* was first recorded by D'Cruz et al., who evaluated the activity of its essential oil against *Ascaris lumbricoides*, a large roundworm infecting a human. The result showed that the paralysis-producing ability of its essential oil was quicker than the standard drug piperazine but slower than tetramisole (D'Cruz, Nimbkark, & Kokate, 1980). Supporting this study Kokate et al., used the volatile oils and their fractions from *P. longum* to test the anthelmintic activity on neuromuscular preparations of *A. lumbricoides*. This study also exhibited that the oil elicited a noticeable effect on the rhythmic movements of *Ascaris*, resulting in partial paralysis that occurred between 12 and 15 min of exposure to oil at 1:1,000 v/v concentration (Kokate, Chaudhari, & Nimbkar, 1980). A separate experiment evaluated the effect of alcoholic fruit extracts against *Toxocara cati* of the cat in vitro. The extract was found to cause cessation of motility and finally death of the worms (Bansod et al., 2005). Singh et al. evaluated the inhibitory effect of the alcoholic extract of the fruits on helminths that showed complete inhibition of gross visual motility of the two flatworms *Gigantocotyle explanatum* and *Fasciola gigantica* (Singh, Kumar, Gupta, & Tandan, 2007). They also observed similar results using essential oil against these two flukes (Singh, Kumar, Tandon, & Mishra, 2010). In another experiment, an alcoholic extract of *P. longum* was used to demonstrate the muscular activity of the parasitic amphistome, *G. explanatum*. The extract caused irreversible paralysis in the amphistome (Singh, Kumar, & Tandan, 2008). Similarly, the essential oil of *P. longum* was also evaluated for its inhibitory effect on the muscular activity of whole *Fasciola gigantica* and strip preparation. The essential oil-induced marked excitatory effect at first and then promoted irreversible flaccid paralysis following 15 min exposure at 3 mg/ml concentration (Singh, Kumar, Tandan, & Mishra, 2009). A recent study evaluated the in vitro ovicidal, larvicidal, and adulticidal activities of the methanol extract and its fractions from the fruits of *P. longum* against gastrointestinal strongyle ova, larvae, and adult amphistomes. The methanol extract was found to be highly active against ova and amphistomes; the n-hexane fraction potentially induced larval mortality while the chloroform fraction was effective against ova, larvae, and adults (Koorse et al., 2018). Adulticidal activity against adult amphistomes was evaluated using methanol extract and its n-hexane, chloroform, n-butanol, and aqueous fractions from the fruits of *P. longum*. Amphistomes were found to be highly sensitive towards the methanol extract while all other extracts/ fractions exhibited moderate anthelmintic activity. The histopathology study revealed morphological changes in tegument, syncytium, and parenchyma (Krishnaprasad et al., 2018).

There is not many reports on the insecticidal and insect repellent activities of *P. longum*. Kokate et al. used the essential oil of *P. longum* to determine its insecticidal activity against four stored-grain insects namely *Bruchus chinensis*, *Sitophilus oryzae*, *Rhyzopertha dominica*, and *Stegobium paniceum*. Promising insecticidal activity of the oil was recorded against *S. oryzae* and *B. chinensis*. The oil also showed significant effect on *R. dominica* and *S. paniceum* (Kokate, Tipnis, & Gonsalves, 1980). In addition, two piperidine alkaloids such as pipernonaline and piperoctadecalidine, isolated from *P. longum*, exerted insecticidal activity against *Spodopteralitura*. Both alkaloids also showed insecticidal activities towards *Myzus persicae* (Park et al., 2002).

Therefore, *P. longum* presents promising therapeutic approaches against helminthic diseases as a potent anthelminthic. However, suitable animal models are needed to further elaborate the efficaciousness and probable toxicity of *P. longum*.

6.9.6 | Acaricidal activity

Acaricidal activity of two alkaloids namely pipernonaline and piperoctadecalidine, isolated from *P. longum* were evaluated against *Tetranychus urticae*. Piperoctadecalidine showed acaricidal activity against *T. urticae* but no such activity was noted for pipernonaline (Park et al., 2002). Ticks and tick-borne diseases are major constraints for the cattle industry and farms in the tropical and subtropical regions including the Indian subcontinent. Ethanol extract of *P. longum* and alcoholic combination with *P. nigrum* exhibited acaricidal property against *Hyalomma anatolicum*. The alcoholic combinations also showed effective acaricidal activity (Singh, Saini, Singh, Sharma, & Rath, 2017). In vitro acaricidal activity of *P. longum* fruit extracts and

their active components were evaluated against *Rhipicephalus* (*Boophilus*) *microplus* ticks. The extract impacted mortality rates of ticks and also affected the reproductive physiology of ticks by inhibiting oviposition; the combination of piperine and piperlonguminine also caused significant mortality in ticks (Godara et al., 2018). The acaricidal activity of the plant represents a unique strategy to combat cattle ticks for proper livestock management.

6.9.7 | Antiamoebic activity

Amoebiasis, a common gastrointestinal disease caused by the protozoan parasite *Entamoeba histolytica* affects approximately 10% of the world's population, mostly in tropical and subtropical countries (Walsh, 1986). Ghoshal and co-workers evaluated the *P. longum* extract and fractions for their efficacy against experimental caecalamoebiasis in rats induced by *E. histolytica*. The ethanol extract, the hexane fraction, and the n-butanol fraction exhibited amoebicidal activity at 1,000 μg/ml concentration whereas the chloroform fraction exhibited the same at 500 μg/ml. The ethanol extract and isolated piperine cured caecal amoebiasis in rats by 90% and 40%, respectively (Ghoshal, Prasad, & Lakshmi, 1996). In another experiment, ethanol extract of roots was used to determine its antiamoebic activity. It was found that the root extract exerted amoebicidal activity in vitro and cured 88% of caecal amoebiasis (Ghoshal & Lakshmi, 2002). Antiamoebic effect of the crude methanol extracts of *P. longum* fruit was evaluated against *E. histolytica* infecting caecum of mice (Sawangjaroen, Sawangjaroen, & Poonpanang, 2004).

Interestingly, many of the experiments depicting antiamoebic activity involve very high doses of the plant extract which limit its probable clinical use. In addition, due to the promising efficiency of the plant against amoebiasis, its mechanism of action must be well elucidated to use the plants as therapeutic against such protozoan parasites.

6.9.8 | Mosquito larvicidal and adulticidal activities

Methanol extract of *P. longum* fruit was studied for mosquito larvicidal activity and it was found to be active against the larvae of *Culex pipienspallens*. The extract containing a piperidine alkaloid, pipernonaline was reported for larvicidal properties (Lee, 2000). Yang et al. examined mosquito larvicidal activity of *P. longum* with the fruit extracted in different solvents and the derived alkaloids against the fourth-instar larvae of the dengue vector *Aedes aegypti*. The crude methanol extract and hexane fraction showed 100% mortality rate against the larvae while pipernonaline showed larvicidal activity (Yang et al., 2002). In another experiment, the efficacy of the ethanol extract was evaluated against fourth instar larvae of *A. aegypti*. The result showed larvicidal efficacy with morphological alterations with extensive damage and shrunken cuticle of the anal papillae (Chaithong et al., 2006). Very recently, the aqueous extract of *P. longum* was recorded for larvicidal as well as ovicidal activity against *A. aegypti*, malarial vector *Anopheles stephensi* and filariasis vector, *Culex quinquefasciatus*. The histo-pathological investigations showed alteration in the mid gut which caused death of the larvae (Dey et al., 2020).

Dose-dependent adulticidal effect of the ethanol extract of *P. longum* was observed against *Stegomyia aegypti*, the key vector of dengue and dengue haemorrhagic fever. The extracts also demonstrated impressive adulticidal activity when tested on female mosquitoes by topical application suggesting it as a potent natural compound to combat against adult mosquitoes (Choochote et al., 2006). Further study is needed to characterize the oil obtained from *P. longum* for mosquitocidal properties.

6.9.9 | Molluscicidal activity

Piper longum was also reported to possess toxic effect on the snail *Indoplanorbis exustus*. The ethanol extract of the fruit singly or in combination with the fruit extracts of *Piper cubeba* and *Tribulus terrestris* showed molluscicidal activity. Single extract of *P. longum* showed significant activity; though, binary extract, that is, *P. longum* + *P. cubeba* and tertiary combination that is, *P. longum* + *P. cubeba* + *T. terrestris* were more effective than the single extract or other combinations (Pandey & Singh, 2009).

Herbal biocides are preferred over chemical biocidal agents because of their less negative impact on the flora, fauna, and the environment. Considering the widespread use, availability, and apparent nontoxicity to larger animals and humans, *P. longum* formulations can be used as antibacterial, antifungal, antiviral, antiprotozoal, insecticidal, and molluscicidal properties as validated by a number of in vitro as well as in vivo experiments. Biocidal activities of *P. longum* are tabulated in Table 8.

6.10 | Miscellaneous biological activities

6.10.1 | Antifertility activity

To evaluate the antifertility activity of *P. longum*, female Sprague Dawley rats were mated with males and fed with ethanol extract and its different solvent fractions from the fruits and the roots and isolated compound piperine after day 1 of pregnancy. The crude extract and hexane fractions of the fruits showed 100% efficacy in terms of the absence of implantations in the ovary (Lakshmi, Kumar, Agarwal, & Dhar, 2006). Antifertility efficacy of *P. longum* and the parameters related to female reproduction were studied using hexane extract of the fruits on female Holtzman rats on their 4-day estrous cycle and after mating. Assessment of the estrous cycle revealed the antifertility and antiimplantation activities of the plant extracts manifested by prolonged estrous cycle length, reduced implantation site number, degeneration of uterine glands and endometrial epithelial cells, reduced levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and also increased estradiol level. Infertility was implicated in the modulation of infertility mediators and gonadotropin insufficiency

TABLE 8 Biocidal activities of *P. longum*

Effect	Extract (isolates)	Active against	Result	Tested concentrations	Reference
Antibacterial effect	Seed oil	*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*	Potent antibacterial activity observed	—	Arambewela et al. (1999)
	Dichloromethane methanol extract of fruit (piperlonguminine, piperine, pellitorine)	*Bacillus subtilis*, *Staphylococcus aureus*, *B. sphaericus*	Three isolates were active against Gram-positive bacteria and moderately ctive against Gram-negative bacteria	0.01–200 μg/ml	Srinivasa Reddy et al. (2001)
	Different solvent extracts	*Staphylococcus albus*, *B. megaterium*, *Salmonella typhi*, *Pseudomonus aeruginosa*, *E. coli*	All extracts showed inhibition zones for almost all bacterial strains	40 μg/disc	Khan and Siddiqui (2007)
	Various solvent extract from fruit	*B. Megaterium*, *streptococcus β-haemolyticus*, *Streptococcus aureus*, *B. subtilis*, *Sarcina lutea*, *E. coli*, *Pseudomonas aeruginosa*, *Shigella sonnei*, *Shigella dysenteriae*, *salmonella typhi*, *Klebsiella species*, *Shigella boydii*, *Shigella flexneriae*	Crude extracts showed mild to moderate activities, ethyl acetate extracts showed relatively better antimicrobial effect, petroleum ether extracts were found to be inactive	40 μg/ml	Ali et al. (2007)
	n-hexane extract of dry roots (isolated piperine,piperlongumine, piperlonguminine,piplartine)	*E. coli*, *P. aeruginosa*, *B. cereus*, *S. typhi*, *Serratia marcescens*, *Staphylococcus aureus*, *Shigella dysenteriae*, *Klebsiella pneumonia*	All isolates showed better inhibition; n-hexane extract showed inhibition zone to only Gram-positive bacteria	100 and 500 mg/ml	Lokhande et al. (2007)
	Aethanol, ethanol and acetonic fruit extract	*Streptococcus mutans*, *Staphylococcus aureus*	All extract showed inhibitory effect against all bacteria	50–0.39 mg/ml	Aneja et al. (2010)
	Methanol extract	*Bacillus subtilis*, *Pseudomonas fluoresces*, *Escherichia coli*, *salmonella typhi*	Showed inhibitory effect against all bacteria	50 μl	Reshmi et al. (2010)
	Root extract (piperlongumine)	*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*	Concentration-dependent susceptibility observed for all strains	25, 50, 100 μg/100 μl	Naika et al. (2010)
	Ethyl acetate, methanol and water extract	*Staphylococcus aureus*, *streptococcus pyogenes and Streptococcus pneumoniae*, *Klebsiella pneumoniae*. *Streptococcus aureus*	All extracts showed high to moderate inhibition zone for all bacteria	0.5 mg/100 μl and 1 mg/100 μl	Sawhney et al. (2011)
	Ethyl acetate, methanol and aqueous extract	*Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus aureus*	All extracts showed antibacterial activity	0.5 mg/100 ml and 1 mg/100 ml	Chauhan et al. (2019)
Anti fungal effect	Hexane fraction of whole plant (pipernonaline)	*Pyricularia oryzae*, *Botrytis cinerea*, *Phytophthora infestans*, *and Puccinia recondita*	Showed potential fungicidal activity	1,000, 500, 250 mg/L	Lee et al. (2001)
	Different solvent extracts	*Aspergillus Niger*	Chloroform, ethyl acetate, acetone and ethanol extract showed antifungal activity	40 μg/disc	Khan and Siddiqui (2007)

(Continues)

TABLE 8 (Continued)

Effect	Extract (isolates)	Active against	Result	Tested concentrations	Reference
	Various solvent extract from stem	*Penecillium sp*, *Aspergillus niger*, *Aspergillus fumigatus*, *Mucor* sp., *Fusarium* sp., *Candida albicans*	All the extracts (except petroleum ether) displayed mild activity against most of the fungi, ethyl acetate extract was active against all the fungal strains	300 μg/10 μl	Ali et al. (2007)
	Methanol, ethanol and acetonic fruit extract	*Candida albicans*, *Saccharomyces cerevisiae*	All extracts showed almost equal inhibition zones for both fungi	50–0.39 mg/ml	Aneja et al. (2010)
Antiparasitic effect	Ayurvedic rasayana preparation	*Giardia lamblia*	98% recovery from infection	900–112 mg/kg	Agarwal et al. (1994)
	Aqueous, ethanol fruit extract	*Giardia lamblia*	100% inhibition of parasite	250 μg/mland 125 μg/ml	Tripathi et al. (1999)
	Fruit extract	*Blastocystis hominis*	50% inhibition of parasite	31.25–1,000 μg/ml	Sawangjaroen et al. (2005)
	Spike ethanol extract	*Leishmania donovani*	Eliminated promastigotes after 48 hr	0.5 mg/ml	Singh et al. (2011)
	n-hexane fraction of fruit (piperlongumide)	*Leishmania donovani*	Activity against promastigotes and axenic amastigotes	100 μg/ml	Ghosal et al. (2012))
Scolicidal activity	Methanolic extract	*Echinococcus granulosus*	Activity against protoscolices of hydatid cysts	25, 50, 100 and 150 mg/ml	Cheraghipour et al. (2021)
Anthemintic activity	Essential oil	*Ascaris lumbricoides*	Paralysed nerve muscle quicker than piperazine but slower than tetramisole	—	D'Cruz et al. (1980)
	Essential oil	*Ascaris lumbricoides*	Inhibited the amplitude of rhythmic contractions, produced partial paralysis	1:1,000 v/v	Kokate, Chaudhari, and Nimbkar (1980)
	Fruit alcoholic extract	*Toxocara cati*	Cause cessation of motility of worms and then caused death	5, 10, 25, 50, 75 and 100 mg/ml	Bansod et al. (2005)
	Fruit alcoholic extract	*Gigantocotyle explanatum*, *Fasciola gigantica*	Complete inhibition of gross visual motility	100, 300, 1,000 and 3,000 μg/ml	Singh et al. (2007))
	Fruit alcoholic extract	*Gigantocotyle explanatum*	Produce non reversible paralysis	100, 300, 1,000 and 3,000 μg/ml	Singh et al. (2008)
	Essential oil	*Fasciola gigantica*	Produced complete irreversible flaccid paralysis	0.1, 0.3, 1.0 and 3.0 mg/ml	Singh et al. (2009)
	Essential oil	*Gigantocotyle explanatum*, *Fasciola gigantica*	Complete inhibition of gross visual motility	100, 300, 1,000 and 3,000 μg/ml	Singh et al. (2010)
	Methanol extract and fractions from fruit	Gastrointestinal Strongyle ova, larvae and adult amphistomes	Methanol extract was most potent against amphistomes and ova; n-hexane fraction induced larval mortality; chloroform fraction was effective against ova, larvae, and also adults	500, 250, 125, 62.5, 31.25, 15.63, 7.81, 3.91, and 1.95 mg/ml	Koorse et al. (2018)
		Adult amphistomes	High sensitivity for methanol extract (IC_{50} of 5.493 mg/ml),moderate	500, 250, 125, 62.5, 31.25, 15.63, 7.81, 3.91 and 1.95 mg/ml	Krishnaprasad et al. (2018)

TABLE 8 (Continued)

Effect	Extract (isolates)	Active against	Result	Tested concentrations	Reference
	Methanolic extract and its n-hexane, chloroform, n-butanol, and aqueous fractions from fruits		activity for other extract/ fractions, morphological changes in tegument, syncytium, and parenchyma		
Insecticidal activity	Essential oil	*Bruchus chinensis*, *Sitophilus oryzae*, *Rhyzopertha dominica*, *Stegobium paniceum*	*S. oryzae* and *B.chinensis* were found to be more vulnerable with LD_{50} 0.182% v/v and 0.464: v/v, respectively	40 mcg/insect	Kokate, Tipnis, and Gonsalves, (1980)
	Fruit methanolic extract (piperoctadecalidine, pipernonaline)	*Spodoptera litura*, *Myzus persicae*	Both alkaloids showed insecticidal activity	0, 100, 250, 500, 1,000 ppm per 10 μl	Park et al. (2002)
Acaricidal property	Fruit methavolic extract (piperoctadecalidine, pipernonaline)	*Tetranychus urticae*	Potent acaricidal activity (LD_{50} = 246 mg/L) only for Piperoctadecalidine	0, 100, 250, 500, 1,000 ppm per 10 μl	Park et al. (2002)
	Ethanol seed extract	*Hyalomma anatolicum*	Acaricidal property with minimum LC50 and LC95 (95% CL) values of 0.071% and 0.135%	—	Singh et al. (2017)
	Fruit extract (piperine, piperlonguminine)	*Rhipicephalus (Boophilus) microplus*	Fruit extract affected mortality and reproductive physiology; 79.2% mortality of ticks by alkaloids	0.27%, 0.55%, and 1.1%	Godara et al. (2018)
Antiamoebic activity	Ethanol extract, hexane fraction, n-butanol, chloroform fraction from fruit and isolated piperine	*Entamoeba histolytica*	All extracts and piperine showed efficacy against experimental caecal amoebiasis of rats	1,000 and 500 μg/ml	Ghoshal et al. (1996)
	Ethanol extract of roots	*Entamoeba histolytica*	Cured 88% of caecal amoebiasis in rats	1,000 μg/ml	Ghoshal and Lakshmi (2002)
	Crude methanol extract of fruit	*Entamoeba histolytica*	Cured 100% of caecal amoebiasis in mice	1,000 mg/kg, 500 and 250 mg/kg/ day	Sawangjaroen et al. (2004)
Mosquito Larvicidal property	Methanol extract fruit (pipernonaline)	*Culex pipiens pallens*	Active against larvae at l0 μg/ml after 24 hr	10 μg/ml	Lee (2000)
	Crude methanol extract and hexane fraction of fruit (pipernonaline)	*Aedes aegypti*	All extract active against larvae; hexane fraction of the methanol extract showed 100% mortality; LC_{50} for pipernonaline 0.25 mg/L	0.06–200 mg/L	Yang et al. (2002)
	Ethanol extract	*Aedes aegypti*	Larvicidal efficacy against 4th instar larvae with LC_{50} value 2.23 ppm	1.5–3.5 ppm	Chaithong et al. (2006)
	Aqueous, petroleum ether, methanol, chloroform extract of leaves	*Aedes aegypti*, *Anopheles stephensi*, *Culex quinquefasciatus*	Lavricidal activity with alterations in the midgut epithelium	10, 25, 50, 100, 250, and 500 ppm	Dey et al. (2020)

(Continues)

TABLE 8 (Continued)

Effect	Extract (isolates)	Active against	Result	Tested concentrations	Reference
Mosquito adulticidal activity	Ethanol extract	*Stegomyia aegypti*	Moderate adulticidal activity with LD_{50} value 0.26 μg/female	0.10–0.50 μg/mg	Choochote et al. (2006)
Molluscicidal activity	Ethanol extract of fruit singly or in combination with fruit extracts of *Piper cubeba* and *Tribulus terrestris*	*Indoplanorbis exustus*	Single extract of *P. longum* showed significant activity; though, binary extract *P. longum* + *P. cubeba* and tertiary combination *P. longum* + *P. cubeba* + *T. terrestris* showed more activity	–	Pandey and Singh (2009)

Note: – indicates not mentioned in the retrieved literature.

(Sarwar et al., 2014). In another experiment, the authors observed spermicidal activity of the hexane extract of the fruits using human sperm in vitro. The study revealed irreversible spermicidal effect, sperm immobilization effect, reduced sperm viability, and reduced hypo-osmotic swelling of the sperm owing to the injury to the sperm plasma membrane (Sarwar, Nirala, Arif, Khillare, & Thakur, 2015). These studies are interesting since the plant is widely accepted as a food crop and a popular spice all over the world. Antifertility and anti-implantation activities exhibited by the plant need further investigation since the plant is consumed regularly as a household spice and caution must be taken in using it in case of expecting mothers or parents planning for children. Otherwise, the plant or its active constituents may be used as herbal antifertility agents as single or adjuvant therapy.

6.10.2 | Cardio-protective and coronary vasodilating activity

The effects of a methanol extract of *P. longum* were investigated on the oxidative stress-induced injury and cellular abnormality in adriamycin (ADR)-induced cardiotoxicity in mice. The extract at two different doses attenuated the ADR-induced decrease in the activities of the marker enzymes aspartate transaminase (AST), alanine transaminase (ALT), LDH and creatine kinase (CK) in the heart and increased their activities in serum. Pre-treatment with the extract also augmented the myocardial antioxidant enzymes like catalase, SOD, GSH-Px, GSH reductase (GR), and GSH which were reduced by the effect of ADE. Histopathological study revealed that the extract treatment reduced degenerative changes and cellular infiltration in the heart and related lesions (Wakade, Shah, Kulkarni, & Juvekar, 2008). The cardio-protective effect of the methanol extract of *P. longum* was also evaluated in an isoproterenol-induced acute myocardial infarction rat model. Oral pre-treatment of methanol extract was found to decrease vascular and fatty degeneration, granular disintegration, and hyaline necrosis of the muscle fibers in histopathological examination. Biochemical observations showed decreased levels of the serum myocardial markers creatine kinase-MB (CKMB) and LDH compared to that of ascorbic acid (Khushbu et al., 2010).

The ethyl acetate soluble portion of the fruit of *P. longum* was investigated for its coronary vasodilating activity on KC1-induced contraction of the rabbit isolated coronary artery. A new amide, dehydropipernonaline isolated from the fruit, was also attributed to the coronary vasodilating activity (Shoji et al., 1986). *Piper longum* is a food, spice as well as a medicinal plant used against stomach disease and analgesia in TCM (Abdubakiev, Li, Lu, Li, & Aisa, 2020). The vessel tension studies demonstrated that piperine, (2E,4E,14Z)-*N*-isobutyleicosa-2,4,14-trienamide, and piperlonguminine from the *P. longum* fruits exhibited remarkable inhibitory properties on phenylephrine-contracted mesenteric artery vasoconstriction. Piperine was recorded to induce the influx of extracellular Ca^{2+} in mesenteric artery smooth muscle cells (MASMCs), by an endothelium-independent mechanism involving the entry of Ca^{2+}. In this study, *P. longum* was suggested as

a promising vascular relaxant with a potential drug candidate against hypertension (Li et al., 2020). Cardioprotective properties of the plant are mainly attributed to its ability to prevent cardiotoxicity, myocardial infarction and to its coronary vasodilating activity. In addition, it has to be determined whether the cardioprotective ability of the plant extract is linked to its ability to attenuate oxidative stress. A few in vivo studies have demonstrated the cardioprotective features of the plant also support the use of the plant; the treatments of heart diseases are recorded from the ancient East Asian literature (Khushbu et al., 2011). However, more elaborate studies are needed in animal models and also using clinical studies to further validate its cardioprotective abilities.

6.10.3 | Vas0-relaxant activity

Li et al. obtained eight compounds from the dry fruits of *P. longum*. Among these, three compounds namely piperine, (2E,4E,14Z)-*N*-isobutyleicosa-2,4,14-trienamide, and piperlonguminine significantly inhibited phenylephrine-induced mesenteric artery vasoconstriction observed by vessel tension studies. Calcium Imaging studies showed that piperine was able to promote the influx of extracellular calcium in MASMCs via an endothelium-independent mechanism involving Ca^{2+} entry suggesting that *P. longum* has great potential as a vascular relaxant for patients with hypertension (Li et al., 2020).

6.10.4 | Antiplatelet activity

Iwashita and co-workers studied the antiplatelet effects of the *P. longum* fruits. Four acidamides namely piperine, pipernonaline, piperoctadecalidine, and piperlongumine, obtained from the fruits were investigated on washed rabbit platelet aggregation induced by collagen, arachidonic acid (AA), and platelet-activating factor (PAF) or thrombin by determination of platelet aggregation, inositol phosphates measurement and receptor binding assay. The result showed inhibition of thromboxane A_2 receptor agonist U46619, inhibition of U46619-induced phosphoinositide hydrolysis, and inhibition of binding of [^{3}H]SQ29548 to thromboxane A_2 receptor. Piperlongumine showed stronger inhibitory effects compared to aspirin, the positive control (Iwashita, Saito, Yamaguchi, Takagaki, & Nakahata, 2007). Isolated compounds piperine, pipernonaline, piperoctadecalidine, and piperlongumine from the fruit demonstrated dose-dependent inhibition on platelet aggregation induced by collagen, AA, and PAF, and the highest activity was attributed to piperlongumine. The authors suggested further investigations to fully understand the mechanism of antiplatelet activity offered by the compounds (Park et al., 2007). So far this is the only work elucidating the antiplatelet effects of *P. longum* fruit-derived acid amides namely piperine, pipernonaline, piperoctadecalidine, and piperlongumine. The results were encouraging and a comparative account of the antiplatelet properties of the crude fruit extract and its active constituents would be an exciting work since the fruits are edible. Besides, it may reveal the enhanced activity of the crude extract over the isolated compounds due to possible synergism among them.

Antiplatelet activity of the plant was demonstrated using a number of different solvents to extract *P. longum* and also by performing the experiment in a dose-dependent manner. However, further studies are needed to elucidate the role of standard drugs and to find out the in vivo as well as ex vivo bleeding time by designing more robust methods to explore the antiplatelet as well as antithrombotic properties (if any) of the plant.

6.10.5 | Melanin inhibitory activity

Min et al. reported *P. Longum* for its inhibitory effect against α-melanocyte-stimulating hormone (α-MSH)-induced melanin production in B16 cells. Piperlongumine isolated from the methanol extract by fractionation was identified as the major melanogenesis inhibitor which showed dose-dependent inhibition (Min et al., 2004). Ethanol extract of the fruits of *P. longum* and the prenylated phenolic compounds bakuchiol, bavachin, and isobavachalcone isolated from fractions were found to exert a potential inhibitory effect against MSH-induced melanin production in B16 mouse melanoma cells. These compounds and the crude extract of the fruits exhibited suppressive effects against pigmentation by melanin in the skin in a dose-dependent manner and may be used as agents for skin whitening (Ohno et al., 2010). A number of compounds extracted from the plant exhibited MSH-induced melanin production in animal models. Since popular fairness creams in the market contain a number of undesirable chemicals with adverse effects on the skin, such herbal alternatives can be used there as possible ingredients.

6.10.6 | Melanin stimulatory activity

Ethanol extract of *P. longum* containing piperine, isopiperine, piperlonguminine, retrofractamide A, retrofractamide C enhanced the melanin content in B16 melanoma cells and also showed a weak stimulative effect on the tyrosinase activity in a concentration-dependent manner. Isopiperine also found to have a strong capacity to increase the tyrosinase activity in a concentration-dependent manner indicating *P. longum* to be a good natural source for skin diseases (Abdubakiev et al., 2020).

6.10.7 | Antiobesity effect

Inhibition of acyl CoA: diacylglycerol acyltransferase (DGAT) has emerged as a potential pharmacological therapy for the treatment of obesity. Chloroform extracts of the fruits of *P. longum* and isolated compounds (2E,4Z,8E)-*N*-[9-(3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl]piperidine, pipernonaline, piperrolein B, and dehydropipernonaline were found to inhibit DGAT using in vitro DGAT inhibitory assay with microsomes from Sprague Dawley rat liver (Lee

et al., 2006). Earlier, the fruit extract demonstrated antidiabetic and lipid-lowering principles. Considering its proven edibility, the efficacy of the fruits can further be investigated as promising antiobesity agents for human use.

6.10.8 | Antiangiogenic activity

Antiangiogenic activity of *P. longum* was studied using B16F-10 melanoma cell-induced capillary formation in C57BL/6 mice. Intraperitoneal administration of the extract at a dose of 10 mg/animal significantly inhibited the number of tumour-directed capillaries. It also regulated the level of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumour necrosis factor (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and the direct endothelial cell proliferating agent vascular endothelial growth factor (VEGF), increased the level of interleukin-2 (IL-2) and tissue inhibitor of metalloprotease-1 (TIMP-1) and inhibited the VEGF-induced vessel sprouting in rats. The extract treatment significantly inhibited the proliferation, cell migration, and capillary-like tube formation of primary cultured human endothelial cells which were implicated in its antiangiogenic activity both in vitro and in vivo (Sunila & Kuttan, 2006).

The antiangiogenic activity of medicinal plants is implicated in their probable application for ailments in which suppression of blood vessel formation is needed, such as macular degeneration, cancer, diabetic retinopathy, and so on. Therefore, the antiangiogenic properties of the plant can further be investigated against such diseases where inhibition of blood vessel formation is desirable. From the above-mentioned studies, *P. longum* was reported to possess unique underlying molecular pathways to modulate the mutual angiogenic signal transduction. However, detailed studies involving animal models are required to establish the dose dependence of its antiangiogenic activity.

6.10.9 | ACE inhibitory activity

Hydroalcoholic extract of the *P. longum* fruits, its fractions and isolated compound piperine were investigated for their angiotensin-converting enzyme (ACE) inhibition activity where hippuryl-L-histidyl-L-leucine (HHL) was used as the substrate. Ethyl acetate and butanol fractions showed the highest inhibitory effect in a concentration-dependent manner justifying its traditional claim as an antihypertensive agents (Chaudhary et al., 2013). However, no use of the standard drug to compare the efficacy and analysis of a single parameter limited the validity of this study. Hence, a robust study design using animal models is needed to obtain reproducible results to establish the cardio-protective effect of *P. longum*.

Since, ACE inhibitors are common medications that decelerators suppress the enzyme ACE, which reduces angiotensin II production and thus reduces blood pressure. *Piper longum* fruits, which have been popularized for its culinary uses, can also be used as a potent food supplement and medication against high blood pressure and associated ailments.

6.10.10 | Radioprotection

The radioprotective property of an ethanol extract of *P. longum* fruits was investigated in Swiss mice with whole-body irradiation. The extract increased the white blood cell (WBC) count in the irradiated control mice from 1,900 to 2,783.3 cells/mm^3. The number of bone marrow cells and α-esterase positive cells was also enhanced by the extract administration compared to the radiation-exposed control animals. In addition, elevated levels of glutathione pyruvate transaminase (GPT), alkaline phosphatase (ALP), and lipid peroxidation (LPO) in the liver and serum were also reduced. Besides, the treatment also increased the reduced GSH production to offer its radio-protective properties probably mediated by antioxidative mechanisms (Sunila & Kuttan, 2005).

6.10.11 | Anti-snake venom activity

Anti-snake venom activities of an ethanol extract of the fruits of *P. longum* and piperine were evaluated against Russell's viper venom in embryonated fertile chicken eggs, mice, and rats. Various models and/or assays were used to investigate the activities like venom lethal and haemorrhagic action (in vitro), venom haemorrhagic action (in vivo), necrotizing action, defibrinogenating action, venom-induced paw oedema, mast cell degranulation, creatine kinase (CK) activity, and catalase activity. Administration of the extract was found to inhibit the venom-induced haemorrhage in embryonated fertile chicken eggs and venom-induced lethality, haemorrhage, necrosis, defibrinogenation, and inflammatory paw oedema in mice in a dose-dependent manner. The extract also reduced the venom-induced mast cell degranulation in rats, reversed the venom-induced decrease in the catalase enzyme level in mice kidney tissue and increased CK levels in mice serum (Shenoy et al., 2013).

These studies indicated that *P. longum* possesses promising antiophidian activities and further examination of its bioactive principles may reveal some chemical antagonists with possible snake venom neutralizing ability. Thus the ethnopharmacological claim of its antiophidian use gains momentum from the above-mentioned experiments. In addition, the plant extract or pure compounds from the plant can be used as adjuvant therapy in snakebite cases in rural India.

6.10.12 | Immunomodulatory activity

Alcoholic extract of *P. longum* fruits and isolated component piperine were studied for their immunomodulatory activity in DLA and EAC-induced Balb/C mice. Administration of the extract and piperine increased the total WBC count to 142.8% and 138.9%, respectively. The number of plaque-forming cells, bone marrow cellularity, and

α-esterase positive cells also increased significantly after immunization (Sunila & Kuttan, 2004). To investigate the immuno-regulatory potential of *P. longum*, an ethyl acetate extract of the fruits and its compound, piperinic acid were evaluated in Balb/C mice treated with sheep red blood cells (RBC) as antigen (in vivo) and human PBMCs (in vitro) models. The result showed dose-dependent decrease of lymphocytes (CD4+ and CD8+ T cells) and cytokine levels in sensitized Balb/C mice. In addition, inhibition of mitogen-induced human peripheral blood mononuclear cells (PBMC) proliferation, mRNA transcripts of IL-2 (ConA) and TNFα, IL-1β, and inducible nitric oxide synthase (iNOS), (LPS) were observed in vitro. Concomitantly, induced NO production was found to be reduced by stimulated macrophages rationalizing the traditional use of *P. longum* against similar disease conditions (Devan, Bani, Suri, Satti, & Qazi, 2007). However, very high concentrations of plant extract exhibiting cytotoxic properties with 100% toxicity to DLA and EAC (Sunila & Kuttan, 2004) are far over than the concentrations that can be translated for human use. Therefore, without the toxicity assessment of such higher doses, it has little value for future studies. Besides, a number of studies have been conducted in rat models to find out the liver-protective ability of the plant extract supporting the traditional use of the plant as a liver-tonic. The most prevalent underlying mechanism of heptoprotection was attributed to its antioxidative potential. However, organized clinical studies are needed to evaluate its hepatoprotective activity for human use. Miscellaneous biological activities of *P. longum* are summarized in Table 9.

7 | *PIPER LONGUM* IN GREEN SYNTHESIS AND NANOTECHNOLOGY

Nanotechnology is an emerging interdisciplinary technique for the synthesis of metal nanoparticles using biological processes. It is gaining significant attention off late for its cost-effective application in biomedicine, material science, bio-sensor, bio-imaging, catalysis, opto-electronics, and so on (Jacob, Finub, & Narayanan, 2012; Reddy, Vali, Rani, & Rani, 2014). A cost-effective and eco-friendly process of synthesis of silver nanoparticles from silver nitrate ($AgNO_3$) with the *P. longum* leaf extract was used as a capping agent and also as a reducing agent. UV–vis absorption spectroscopy, scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (FTIR) characterized the nanoparticles which further exhibited significant cytotoxic activity on the HepG2 cell line (Jacob et al., 2012). Aqueous extract of the fruit was used to synthesize silver nanoparticles which were also characterized by UV–Vis, SEM, FTIR, and dynamic light scattering (DLS) particle size analyser. These silver nanoparticles (PLAgNPs) showed excellent in vitro antioxidant activity as well as cytotoxic effect against MCF-7 breast cancer cell lines and also exhibited potent biocidal activity against *B. subtilis*, *B. cereus*, *S. aureus*, and *P. aeruginosa* (Reddy et al., 2014). Green synthesis of gold nanoparticles (AuNPs) was achieved by reducing aqueous gold ions using *P. longum* leaf extract. UV–Vis spectroscopy characterized the nanoparticles; selected area electron diffraction (SAED) and X-ray diffraction found its crystalline structure; transmission electron microscopy (TEM) identified the morphology and FTIR and Raman spectroscopy identified the water-soluble bio-molecules (Mallikarjuna et al., 2015). Nakkala et al., also synthesized gold nanoparticles (PLAuNPs) using the fruit extract. Characteristics were confirmed by UV–vis spectroscopy; size, shape, capping and reduction, and thermal stability were confirmed by DLS, TEM-EDX, FTIR, and thermogravimetric analysis (TGA), respectively. These nanoparticles showed moderate in vitro antioxidant activity and potent catalytic activity which may be exploited as clearing agents for the toxic dyes in industrial effluents (Nakkala, Mata, & Sadras, 2016). In addition, palladium nanoparticles (PdNPs) were synthesized using the fruit extracts and were found as effective catalysts for amine-, ligand-, and copper-free Sonogashira coupling reaction, characterized by UV–vis, FTIR, and TEM methods (Nasrollahzadeh, Sajadi, Maham, & Ehsani, 2015). Silver nanoparticles (AgNPs) with potent antioxidant, radical scavenging, anticancer (against Hela cell line), and larvicidal (against *A. stephensi*, *Aedes aegypti*, and *Mesocyclops thermocyclopoide*) activities were synthesized using aqueous extract of *P. longum* leaves, characterized by UV–Vis, FE-SEM, XRD, and FTIRI (Yadav, Saini, Kumar, Pasi, & Agrawal, 2019). Cost-effective synthesis of silver nanoparticles using *P. longum* catkin extract showed catalytic and antibacterial activities against mastitis-causing bacteria *S. aureus*, *P. aeruginosa*, and *B. subtilis* (Jayapriya et al., 2019) and food-borne pathogenic bacteria namely *B. cereus*, *S. aureus*, *E. coli*, *Proteus mirabilis*, *K. pneumoniae*, *P. aeruginosa*, and *S. typhi* (Huang et al., 2020). *Piper longum* catkin extract was also used to synthesize silver nanoparticles as well as copper oxide and nickel nanoparticles which exhibited anticancer, antioxidant, antimicrobial, and redox catalytic activities, characterized by UV–Vis, FTIR, SEM, and atomic force microscopy (AFM) (Jamila et al., 2020). These experiments support the advantages of using simple and cost-effective bio-green synthesis methods for manufacturing different metal nanoparticles with potent antioxidant, antimicrobial, catalytic, and cytotoxic activities which may be used for pharmaceutical and industrial purposes.

8 | CLINICAL STUDIES

In the Indian traditional system of medicine, *P. longum* is used for prophylactic treatment of asthma and is found to decrease the frequency and severity of asthma attacks in children. Dahanukar et al. studied the antiallergic efficacy of *P. longum* in children to understand its dose and mode of action. They selected 20 paediatric patients suffering from asthma. The study was carried out to test the sensitivity towards house dust mite extract using *P. longum* in children under and over 5 years. Serum IgE tests, pulmonary function, and asthma gradation were assessed and repeated every week. After completion of the 5th week, the results showed significant improvement in the asthma patients. One year of treatment exhibited excellent response in 11 patients, moderate response in three patients, and no satisfactory result in the remaining three patients (Dahanukar, Karandikar, & Desai, 1984). Though there are some reports on clinical studies on Ayurvedic formulations containing the plant as a minor component,

TABLE 9 Miscellaneous biological activities of *P. longum*

Activity	Parts used/ extracts	Effective compounds	Tested concentrations	In vitro/in vivo	Model	Experimental design	Results/mechanism of action	References
Antifertility activity	Ethanol extract and different solvent fractions from fruits	Piperine	200 mg/kg	In vivo	Mated female Sprague Dawley rats	Antifertility bioassay method	100% efficacy with crude ethanol extract and hexane fraction	Lakshmi et al. (2006)
	Hexane extract of fruit	–	150 and 250 mg/kg		Female Holtzman rats on fourday estrous cycle and after mating	Assessment of estrous cycle, antifertility and antiimplantation activities	Length of estrous cycle ↑, implantation site number ↓, degeneration of uterine glands and endometrial epithelial cells, levels of LH and FSH ↓, estradiol level ↑	Sarwar et al. (2014)
	Hexane extract of fruits	–	1, 5, 10, 15 and 20 mg/ml	In vitro	Study with human sperms	Sperm immobilization assay	Irreversible spermicidal effects, sperm immobilization effect, sperm viability ↓, injury to sperm plasma membrane	Sarwar, Nirala, Arif, Khillare, & Thakur, (2015)
Cardio-protective activity	Methanol extract	–	250 and 500 mg/kg	In vivo	Acute myocardial infarction, induced by isoproterenol in rats	Histopathological examination, biochemical investigation	Vascular and fatty degeneration ↓, granular disintegration, and hyaline necrosis of muscle fibers; levels of CK-MB and LDH ↓	Khushbu et al. (2010)
	Methanol extract of fruits	–	250 and 500 mg/kg	In vivo	Tissue peroxide damage and adriamycin-induced cardiotoxicity in Wistar rats	Biochemical and histopathological studies	Maintained levels of AST, ALT, LDH, and CK in the heart; regulated myocardial antioxidant enzymes, degenerative changes, and cellular infiltration in the heart ↓	Wakade et al. (2008)

TABLE 9 (Continued)

Activity	Parts used/ extracts	Effective compounds	Tested concentrations	In vitro/in vivo	Model	Experimental design	Results/mechanism of action	References
Coronary vasodilating activity	Fruit extract	Dehydropipernonaline	—	In vivo	KCl-induced contraction of the rabbit isolated coronary artery	Histopathological examination, biochemical investigation	Coronary vasorelaxant activity	Shoji et al. (1986)
Vaso-relaxant activity	Fruit extract	Piperine, (2E,4E,14Z)-*N*-isobutyleicosa-2,4,14-trienamide, and Piperlonguminine	10^{-8}, 10^{-7}, 3×10^{-7}, 5×10^{-7}, and 106 M	In vivo	Phenylephrine-induced mesenteric artery vasoconstriction	Calcium imaging studies	Influx of Ca^{2+} in MASMCs via endothelium-independent mechanism	Li et al. (2020)
Antiplatelet activity	Aqueous, ethanol and butanol extract of fruits	—	100 mg/ml	In vitro	Rabbit platelet aggregation induced by collagen, arachidonic acid and platelet-activating factor or thrombin	Determination of platelet aggregation, inositol phosphates measurement and receptor binding assay	Thromboxane A_2 receptor agonist U46619 ↓, i U46619-induced phosphoinositide hydrolysis ↓, binding of [^{3}H] SQ29548 to thromboxane A_2 receptor ↓	Iwashita et al. (2007)
	Fruit extract	Piperine, pipernonaline, piperoctadecalidin, piperlongumine	30, 150, and 300 μM	In vitro	Rabbit platelet	Determination of platelet aggregation	Dose-dependent inhibitory activities on platelet aggregation induced by collagen, arachidonic acid and PAF	Park et al. (2007)
Melanin inhibitory activity	Methanol extract from fruits	Piperlongumine	25, 12.5, 6.3, and 3.1 μM	In vitro	α-MSH-induced melanin production in B16 cells	Measurement of melanin depigmentation	Showed dose dependant inhibitory effect with IC_{50} value of 9.6 μM	Min et al. (2004)
	Ethanol extract of fruits	Bakuchiol, bavachin, isobavachalcone	—	In vivo	α-MSH-induced melanin production in B16 mouse melanoma cells	In situ melanin assay and MTT assay	All compounds and the crude extract had suppressive effects against pigmentation by melanin in the skin	Ohno et al. (2010)
Melanin stimulation activity	Ethanol extract	Piperine, isopiperine, piperlonguminine, retrofractamide A, retrofractamide C	1, 10, and 50 μl	In vitro	B16 melanoma cells	—	Increased the melanin content and tyrosinase activity	Abdubakiev et al. (2020)

(Continues)

TABLE 9 (Continued)

Activity	Parts used/ extracts	Effective compounds	Tested concentrations	In vitro/in vivo	Model	Experimental design	Results/mechanism of action	References
Antiobesity activity	Chloroform extract of fruits	(2E,4Z,8E)-*N*-[9-(3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl]piperidine, pipernonaline, piperrolein B, dehydropipernonaline	—	In vivo	Microsomes from Sprague Dawley rat liver	Measurement of in vitro DGAT activity	Potential DGAT inhibitory activity; IC_{50} value varied from 21.2 to 37.2 compared to kuraridine	Lee et al. (2006)
Antiangiogenic activity	Alcoholic extract of fruits	—	10, 5, and 1 μg/ ml	In vitro	Determination of angiogenesis, quantitation of gene-specific mRNA of VEGF, endothelial cell migration assay, tube formation assay	B16F-10 melanoma cell-induced capillary formation in C57BL/6 mice, human umbilical vein endothelial cells (HUVECs)	Inhibited (50.6%) the number of tumour-directed capillaries, regulate the level of cytokines such as IL-1 hr, IL-6, TNF-a, GM-CSF, level of IL-2, and tissue inhibitor of metalloprotease-1 (TIMP-1) increased, inhibited the VEGF-induced vessel sprouting	Sunila and Kuttan (2006)
Angiotensin converting enzyme (ACE) inhibitory activity	Hydroalcoholic extract of fruits, and fraction	Piperine	50–500 μg/ml	—	—	Hippuryl-L-histidyl-L-leucine used as substrate	Ethyl acetate and butanol fractions showed highest inhibitory effect in a concentration-dependant manner with IC_{50} values of 1.40 and 1.75 mg/ml respectively	Chaudhary et al. (2013)
Radio-protective activity	Ethanol extract of fruits	—	100 mg/kg	In vivo	Whole body irradiated Swiss mice	Effect of extract on bone marrow cellularity and α-esterase activity, on radiation-induced toxicity	Increased the WBC count, number of bone marrow cells and α-esterase positive cells, reduced the elevated levels of GPT, ALP, and LPO in liver and serum, increased the reduced GSH production	Sunila and Kuttan (2005)

TABLE 9 (Continued)

Activity	Parts used/ extracts	Effective compounds	Tested concentrations	In vitro/in vivo	Model	Experimental design	Results/mechanism of action	References
Anti-snake venom activity	Ethanol extract of fruit	Piperine	50 and 500 mg/ml; 0.3 and 3 mg/ml	In vivo and in vitro both	Russell's viper venom in embryonated fertile chicken eggs, mice and rats	Venom lethal and haemorrhagic action (in vitro), venom haemorrhagic action (in vivo), necrotizing action, defibrinogenating action, venom-induced paw oedema, mast cell degranulation, CK assay and assay for catalase activity	Inhibited haemorrhage in eggs, lethality, haemorrhage, necrosis, defibrinogenation and inflammatory paw oedema in mice, mast cell degranulation in rats; maintained catalase enzyme and CK enzyme levels in mice	Shenoy et al. (2013)
Immunomodulatory activity	Methanol extract of fruit	Piperine	500, 250, 100, and 50 μg/ml	In vivo	DLA and EACinduced Balb/C mice	Effect on haematological parameters, bone marrow cellularity, and α-esterase positive cells number, circulating antibody titre, plaque-forming cells in spleen	Increased the total WBC count, number of plaque-forming cells also enhanced, bone marrow cellularity and α -esterase positive cells were also increased	Sunila and Kuttan (2004)
	Ethyl acetate extract of fruits	Piperinic acid	10, 20, 40 and 80 mg/kg	Both and in vitro	Balb/C mice treated with sheep RBCs as antigen (in vivo) and human PBMCs (in vitro) models.	Lymphocyte immunophenotyping, intracellular cytokine estimation, [3H] thymidine incorporation assay, MTT assay, assay for nitrite determination	Dose dependent decrease of lymphocytes (CD4+ and CD8+ T cells) and cytokine levels; inhibition of mitogen-induced PBMC proliferation, mRNA transcripts of IL-2 (ConA) and TNFα, IL-1β, and iNOS (LPS); NO production reduced by stimulated macrophages	Devan et al. (2007)

Note: — indicates not mentioned in the retrieved literature.

pharmacological investigations on clinical aspects of *P. nigrum* extracts or isolated compounds are still lacking. Therefore, randomized, double-blind, and placebo-controlled clinical studies are needed to formulate its dose, to elucidate its possible mode of action and to assess its toxic attributes in humans.

9 | TOXICITY PROFILE

Piper longum is extensively used in traditional medicine as well as a common spice for culinary purposes indicating its apparent safety in humans. In one study, acute and chronic oral toxicity assessment of the ethanol extract of *P. longum* fruits was carried out in mice with acute dosages of 0.5, 1.0, and 3 g/kg for 24 hr and chronic dosage of 100 mg/kg/day for 90 days. The extract caused no significant acute or chronic mortality, and no significant change in the pre- and post-treatment body weight. However, it caused a significant increase in the weight of the lungs and spleen and induced a noteworthy enhancement in reproductive organ weights, sperm motility, sperm count, and failed to elicit any spermatotoxic effect in the treated animals compared to the control (Shah, Al-Shareef, Ageel, & Qureshi, 1998). *Piper longum*is widely used as the main ingredient of "Trikatu," a generic herbal formulation depicted in the Indian system of medicine. The acute and sub-acute toxicity study of "Trikatu" was performed on Charles Foster rats at a dose of 2,000 mg/kg b.w. once and at doses of 5, 50, and 300 mg/kg b.w. for 28 days. In the acute experiment, no significant changes were observed in mortality, morbidity, gross pathology, weight gain, organ weight, hematological (WBC and RBC count), and biochemical profile (serum creatinine, SGOT, SGPT, lipid, GSH, and MDA content). Moreover, subacute experiments did not exhibit any significant changes except for an increase in LDL, SGPT, and a decrease in WBC and high-density lipoproteins HDL (Chanda et al., 2009). Acute (14 days), subacute (28 days), and chronic (90 days) toxicity of *P. longum* fruit extract were also studied in albino rats. No significant mortality, the difference in body weight and vital organ weight were observed by the administration of the extract; but there was a significant increase in SGPT, creatinine, and bilirubin content and significant damage in the cells of liver, kidney, testis, gastric mucosa, and intestinal mucosa (Sabhahit, 2010). It was further observed that long pepper at a dose of 1 g/kg body weight demonstrated the properties of an effective contraceptive agent without any toxic or teratogenic effects. Therefore, avoidance of its use during pregnancy and lactation was suggested (Das, Sarkar, & Thakur, 1987).

10 | *PIPER LONGUM* AS BIOAVAILABILITY ENHANCER

The bioavailability term is used to indicate the fraction of a dose that is orally administered and reaches the systemic circulation as an intact drug, then absorption and degradation occur with the help of local metabolites. The bioavailability of orally administered drugs is calculated by the ratio of the area under the curve (AUC) against the area for intravenous administration of the particular drug. Boswellic acids are well-known natural products, which have the capacity to retard inflammation effectively without any severe adverse effects. Bioactivity and the therapeutic uses of boswellic acidare restricted owing to its poor pharmacokinetic properties. *Piper longum* extract was found to increase the bioavailability of boswellic acid ($p < .05$). The results confirmed that *P. longum* may be administered orally with boswellic acid together for effective therapeutic efficacy (Vijayarani et al., 2020). Oxytetracycline (OTC) is used for the treatment of various bacterial, rickettsial, and mycoplasmal infections of poultry and other avian species. Pre-treatment with *P. longum* was found to enhance the bioavailability of OTC when administered orally in white Leghorn hens. The plasma OTC concentrations were studied using the microbial assay technique using *Bacillus cereus* var. *mycoides* as the test organism. The pharmacokinetic data revealed that *P. longum* pre-treated animals demonstrated significantly higher AUC, area under the first moment of plasma drug concentration-time curve, and mean residential time (Singh, Varshneya, Telang, & Srivastava, 2005). Phenytoin, a widely used antiepileptic drug has a low therapeutic potential with side effects. Rats were administered with 200 mg powder of *P. longum* alongside 0.5 ml of suspension containing 10 mg phenytoin for 5 days orally. Phenytoin in blood serum was estimated and it was found that the illustrated AUC was more in rats treated with *P. longum* along with Phenytoin as compared to rats given only Phenytoin (Wanjari et al., 2020).

11 | CONCLUSIONS AND PERSPECTIVES

Piper longum or long pepper, a world-known spice mostly used for household cooking purposes or seasoning is mentioned in various traditional and folkloric medicinal systems for its widespread use in multiple disease treatments. Researchers have demonstrated the remarkable effects of *P. longum* against a plethora of disease conditions, including cancer, inflammation, depression, diabetes, obesity, cardiac disease, and liver ailments. The plant has also demonstrated potent inhibitory properties against microbial infections and insects and offered protection against the effects of radiation. In addition, the plant was extensively reported for its antioxidant, antiplatelet, antifertility, and immunomodulatory effects. However, its common traditional uses against insomnia, dementia, epilepsy, convulsions, asthma, and rheumatoid arthritis have been validated by limited scientific evidences. The bioactive constituents revealed the presence of alkaloids, lignans, volatile oil, organic acids, and esters in different parts of this plant. The pharmacological attributes of *P. longum* are primarily credited to piperine, which possesses a varied range of bioactivities (Chinta, Syed, Coumar, & Periyasamy, 2015). However, *P. longum* houses a huge range of phytochemicals many of which are yet to be identified, characterized, and assessed for bioactivity.

Although long pepper has an enormous world-wide demand owing to its array of medicinal properties, very little attention has been paid to its commercial production, cultivation, and exportation

which is not well established till date. Other shortcomings in this regard include a lack of bioactivity-guided isolation, chemical characterization, and structure–activity studies of the isolated phytochemicals as well as sparse clinical studies and very few toxicological reports. In addition, synergistic activity of *P. longum* extract in bi- or poly-herbal formulations has not been well elucidated. Clinical studies on this plant extract or formulations have been carried out against asthma. However, well-designed randomized, double-blind, and placebo-controlled clinical studies are needed to validate its widespread pharmacological properties for human use. Most of the toxicological analyses were performed in animal models and no safe dose was mentioned for human use. However, due to its widespread culinary uses, the plant is considered safe and is used in many traditional polyherbal formulations in varying doses. The plant is easily available, inexpensive, and appears to be nontoxic, as no mortality and morbidity have been reported with the use of high doses of various solvent extracts. Therefore, it can be concluded that long pepper is safe and effective when used against human medical conditions. However, the pharmacokinetics of the plant extracts and the active principles and their ability to penetrate BBB in the case of neurological applications are still an enigma. Therefore, the existing research gaps in the toxicological studies and pharmacokinetics in humans are also needed to be substantiated. With the advent of modern analytical tools, molecular docking, network pharmacology, and omics approaches, these limitations can be overcome to accept this age-old and popular medicinal plant in the treatment of various human medical conditions.

AUTHOR CONTRIBUTIONS

PB, MG, TM, and AVG retrieved the literature and compiled and revised the first and the second draft and also prepared the tables. DR, ABM, AM and ND retrieved the extra literature during revision and VMM, MTP, MHR and NKJ prepared the revised draft. GESB, SCS, MSS and R helped in softwares and drawings. MK, DKP and AD supervised the overall content.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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MINI-REVIEW

Approaches for in vitro propagation and production of plumbagin in *Plumbago* spp.

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Abstract

The genus *Plumbago* (family *Plumbaginaceae*), commonly known as leadwort, is a sub-tropical shrub that produces secondary metabolite plumbagin, which is employed by pharmaceutical companies and in clinical research. Plumbagin is a potent pharmaceutical because of its anti-microbial, anti-malarial, antifungal, anti-inflammatory, anti-carcinogenic, anti-fertility, anti-plasmodium, antioxidant, anti-diabetic, and other effects. This review documents the biotechnological innovations used to produce plumbagin. The use of modern biotechnological techniques can lead to a variety of benefits, including better yield, increased extraction efficiency, mass production of plantlets, genetic stability, increased biomass, and more. Large-scale in vitro propagation is necessary to minimize over-exploitation of the natural population and allow the use of various biotechnological techniques to improve the plant species and secondary metabolite production. During in vitro culture, optimum conditions are requisites for explant inoculation and plant regeneration. In this review, we provide information on various aspects of plumbagin, depicting its structure, biosynthesis, and biotechnological aspects (both conventional and advanced) along with the future prospects.

Key Points

- *Critical assessment on in vitro biotechnology in Plumbago species*
- *In vitro propagation of Plumbago and elicitation of plumbagin*
- *Biosynthesis and sustainable production of plumbagin*

Keywords Plumbagin · *Plumbago* · Micropropagation · Elicitation · In vitro propagation

Introduction

The World Health Organization estimates that over 80% of the world's population living in developing countries rely heavily on plant-based medicines (WHO 2022, https://www.who.int/news/item/25-03-2022-who-establishes-the-global-centre-for-traditional-medicine-in-india). Secondary metabolites are primarily produced by plants' defense mechanisms in response to pathogen attacks (Erb and Kliebenstein 2020). Plants that produce secondary metabolites are employed in pharmaceutical preparations (Seca and Pinto 2018). The functional genomics and genes linked with

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plant secondary metabolism are poorly understood. Plants are assumed to function as chemical factories, producing a wide range of structurally diverse bioactive secondary metabolites. Isolating bioactive compounds from whole plants places a strain on natural germplasm. Furthermore, manmade activities and natural calamities are all contributing to the deterioration of the earth's flora. The list of endangered medicinal plant species is increasing. So, researchers have developed alternate approaches for conserving medicinal plants in the wild, such as controlled cultivation, in vitro growth, plant tissue culture, ex situ and in situ conservation tactics, encapsulation techniques, and genetic libraries. Napthoquinones are naturally occurring phenolic compounds that are found in plants as well as some bacteria, fungi, actinomycetes, and lichens.

Plumbagin (5-hydroxy-2-methyl-1, 4-napthoquinone) is the most common napthoquinone, named after the *Plumbago* genus from which it was isolated (van der Vijver 1972). The Indian subcontinent uses roughly 7 metric tonnes of plumbagin every year (Gangopadhyay et al. 2011a, b; Patel et al. 2022). The roots of *Plumbago* spp. have high demand on both the domestic and foreign markets (Muche et al. 2022). *Plumbaginaceae is a family of flowering plants that includes 10–20 species of Plumbago spp.* (Ye et al. 2022). It is native to warm temperate and tropical climate zones around the world (Priyanjani et al. 2021). In addition to herbal extract blends, the roots of *Plumbago* are active constituents in over 30 ayurvedic preparations (Choudhary et al. 2021; Al-Harrasi et al. 2023). The roots are used in Ayurveda formulations such as Chitrakasavam, Chitrakachurnam, Dasamularistam, Gulgulutiktakam, Yogarajachurnam Kumaryasawaya, Pippalyasawaya, Mahamasha massage oil, Hinguvachadi, Indukanta, Trimada, and Yogaraja guggulu only after being purified/cured to reduce toxicity, and several traditional purification processes have been described (Akhilraj and Rukmini 2021; Kar et al. 2021; Shukla et al. 2021; Al-Harrasi et al. 2023).

Pharmaceutical companies exploit *Plumbago* extensively and unrestrained to satisfy their ongoing needs, resulting in a significant population decline in the wild. The natural population of *Plumbago* through seed is possible, but it is ineffective due to the low germination percentage required to meet the demand for propagating the high plumbagin-containing population. Furthermore, unrestricted destructive harvesting of *Plumbago* from wild populations causes this plant to become extinct before seed set (Sharma and Thakur 2020; https://www.iucnredlist.org/search/list?query=plumbago&searchType=species). The above-mentioned constraint can be overcome by in vitro culturing of *Plumbago* species, which allows for the application of various biotechnological approaches to overcome production and harvesting issues. Micro-propagation of beneficial plant species efficiently yields plant material in a short period of time, allowing bioactive assays and pharmacological research.

In vitro propagation allows for a continual supply of secondary metabolites despite the slow growth of *Plumbago* species and the time necessary to extract plumbagin (Beigmohamadi et al. 2021). Plumbagin accumulates in plant cells in response to biotic and abiotic stressors (Jaisi and Panichayupakaranant 2020). Elicitor concentrations, exposure times, and age or stage of the culture at the time of elicitor treatment all have a significant impact on the successful creation of biomass and the accumulation of plumbagin (Komaraiah et al. 2002). In vitro techniques like micropropagation are increasingly being used to conserve agricultural genetic resources, particularly for crops that are vegetatively propagated, have difficult-to-germinate seeds, or cannot be kept in a typical horticulture. Many agricultural, horticultural, and medicinal plants, as well as significant crops, have been propagated in vitro (Madzikane et al. 2022). This mini-review aims to provide an up-to-date overview of various aspects of in vitro propagation and plumbagin production in various *Plumbago* species, with notes on its occurrence, biosynthesis, endophytes mediated production of plumbagin, micropropagation, organogenesis, *Agrobacterium*-mediated transformation, precursor feeding, and genetic diversity assessment.

Natural occurrence of plumbagin

Plumbagin was isolated for the first time in 1829. Plumbagin is a napthoquinone found in several plant families, including the *Balsaminaceae*, *Droseraceae*, *Euphorbiaceae*, *Nepenthacea*, and *Plumbaginaceae* (Rahman-Soad et al. 2021; Christensen 2018). The shoot apex was found to have the highest plumbagin content, and the petiole had the lowest. Roots of *Plumbago rosea* L. reportedly contain the highest amount of plumbagin followed by the leaves of *P. auriculate* and the stem of *Plumbago zeylanica* L. (Usmani et al. 2020). In addition to *Plumbago indica* L., *Plumbago auriculata* Lam., *Plumbago europaea* L., *Plumbago pulchella* Boiss., and *P. zeylanica*, there are several more species of the plant. *P. europaea*, *P. rosea*, and *P. zeylanica* roots are now the most widely used source of plumbagin. *P. rosea* roots are the highest, followed by that of *P. auriculate* leaves and *P. zeylanica* stems. The roots of *P. rosea* collect the most plumbagin, although the leaf and stem sections of *P. auriculata* and *P. zeylanica* produce the highest quantities (Mallavadhani et al. 2002). Figures 1 and 2 show the distribution and various species of the *Plumbago* genus, respectively.

Structure and biosynthesis of plumbagin

Structure

Plumbagin ($C_{11}H_8O_3$) (5-hydroxy-2-methyl-3,4-naphthoquinone) (Fig. 2e) is a yellow pigment which is highly soluble

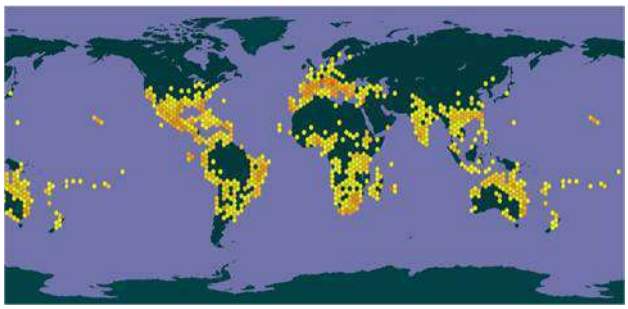

Fig. 1 Worldwide distribution of *Plumbago* (source: https://www.gbif.org/species/3082281)

in alcohol, acetone, chloroform, benzene, and acetic acid and slightly soluble in hot water (Babula et al. 2009). Plumbagin can be toxic to normal body cells when administered in a higher dose (Sumsakul et al. 2016). In order to avoid toxicity, a metal complex [Cu(PLN)(PHEN)]NO_3 was formulated which was found to intercalate and cleave DNA effectively (Padumadasa et al. 2016).

Biosynthesis of plumbagin

The plumbagin is synthesized via the acetate and polymalonate pathways (Fig. 3) (Muralidharan et al. 2020). There are numerous unidentified intermediate stages that lead to *Plumbago* synthesis (Muralidharan et al. 2020). Acetate feeding experiments with precursors being integrated into plumbagin on young shoots of *P. europaea* L. were conducted to show how the plumbagin biosynthetic process works. To determine if the plumbagin was tagged or not, it was chemically broken down. According to the findings, plumbagin is synthesized through the polyacetate-malonate route, and type III polyketide synthase is responsible for six

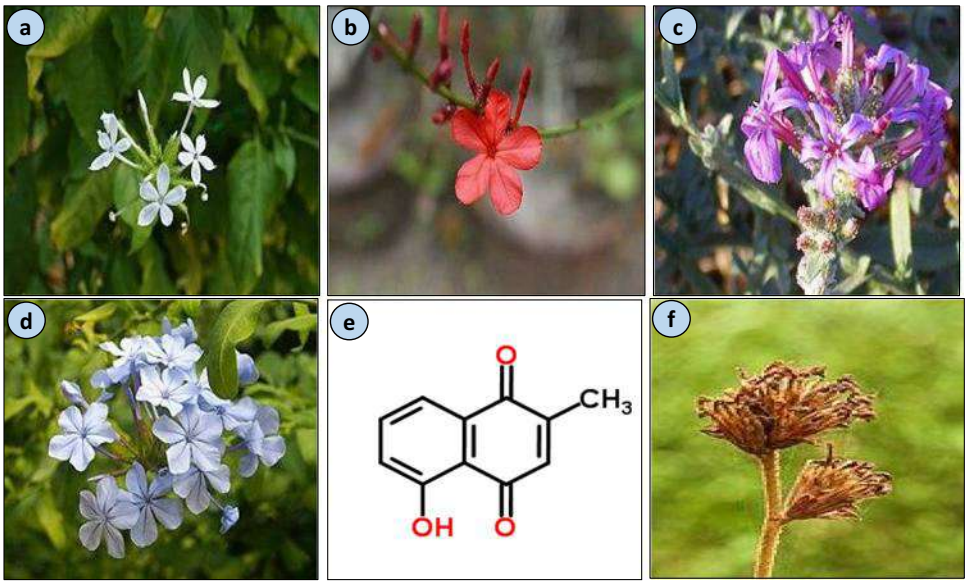

Fig. 2 Different species of *Plumbago*. **a** *Plumbago zeylanica* (source: Wikimedia commons; Creative Commons Attribution-Share Alike 3.0). **b** *Plumbago indica* (source: Wikimedia commons; Creative Commons Attribution 4.0). **c** *Plumbago europaea* (source: Wikimedia commons; Public domain). **d** *Plumbago auriculata* (source: Wikimedia commons; Creative Commons Attribution-Share Alike 4.0). **e** Chemical structure of plumbagin (source: http://www.chemspider.com/). **f** *Plumbago auriculata* seeds (source: Wikimedia commons; Creative Commons Attribution-Share Alike 4.0)

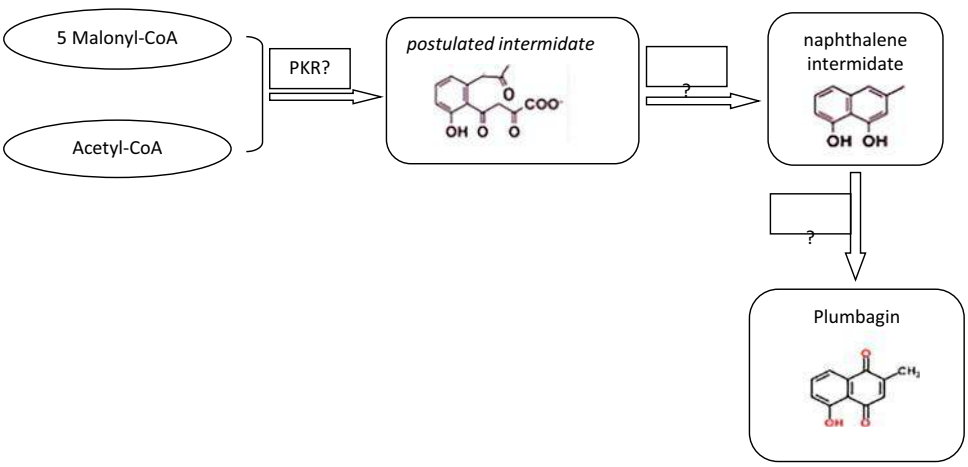

Fig. 3 The acetate-polymalonate pathway. PKR polyketide reductase

condensations of malonyl-CoA that lead to the formation of the basic molecule (Springob et al. 2007). It is known that the plumbagin biosynthetic pathway contains polyketide synthase (PKS). So far, only polyketide synthase (PKS) from the plumbagin biosynthetic pathway has been identified and studied. This polyketide synthase, a member of the hexaketide synthase family, generates hexaketide intermediate structures from acetyl- and malonyl-CoA. The acetate-polymalonate process uses one acetyl-CoA and five malonyl-CoA molecules to form the naphthoquinone skeleton of plumbagin. The first committed step in the formation of plumbagin is catalyzed by the type III PKS enzyme through the repeated condensation of acetate and polymalonate. (Jadhav et al. 2014). Cytochrome *P450*s (CYPs) catalyze the hydroxylation, oxidation, hydration, and dehydration steps that intermediate molecules go through as part of the production of plumbagin. The enzymes responsible for catalyzing the uncharacterized events in the route of plumbagin biosynthesis are currently unknown. Transcriptome and metabolomic profiling of plumbagin by Vasav et al. (2020) suggests that the Aldo-ketoreductase, Cyclase, *PzCYP81B140*, and PzCYP81B141 from cyto-chrome *P450* family could be the potential candidate genes involved in the plumbagin biosynthesis (Vasav et al. 2020). Plumbagin is formed via the hydroxylation and oxidation of 3-methyl-1,8-naphthalene-diol and isoshinanolone catalyzed by CYP81B140 and CYP81B141 (Vasav et al. 2022). Isoshinanolone and 3-methyl-1–8 naphthalene diol may be plumbagin's likely antecedents. According to one research, the enzyme naphthoate synthase is responsible for catalyzing the cyclization of O-malonyl benzoyl CoA in order to create an intermediate that is then processed by thioesterase to produce plumbagin. Using research on quantum mechanics, two potential structures for this intermediate were proposed (Muralidharan et al. 2020). The diagrammatic biosynthetic route for plumbagin is shown in Fig. 4.

In vitro propagation and plumbagin production in various *Plumbago* species

Plumbagin content was found to vary depending on the plant species and plant part from which it was isolated. Since the root-specific accumulation of plumbagin was noted in *P. rosea* (Sharma and Agrawal 2018) and *P. zeylanica*, in vitro root culture may serve as an exciting option as an alternate source of plumbagin production. Plants propagated by tissue technique are more cost-effective (Cardoso et al. 2019). The plant is preferably propagated by vegetative techniques. Hence, in vitro propagation has been proved to be an effective tool as it recruits the vegetative mode of reproduction. In vitro cultures enable the mass production of plants and also aid to the conservation of many endangered and other economically important plants. Due to the declining number of wild populations of *Plumbago* species, the development of alternative techniques to conserve the plant as well as to produce plumbagin sustainably is absolutely necessary. *P. europaea* seed propagation is difficult due to poor seed quality, low germination rate, and low seedling survival

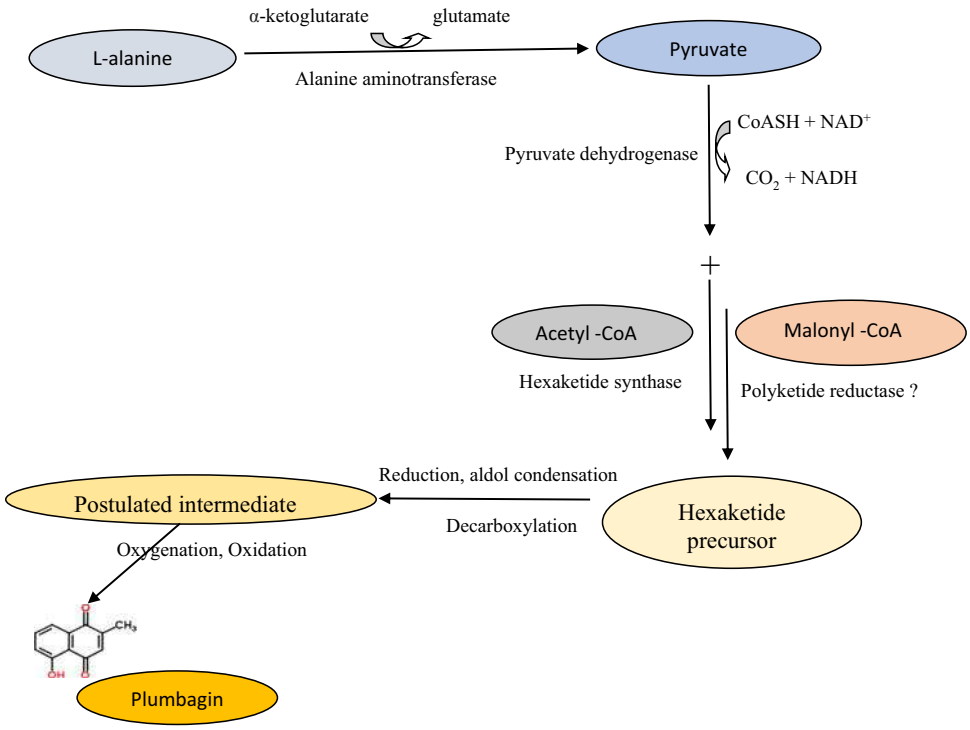

Fig. 4 Biosynthetic pathway of plumbagin through L-alanine (Jaisi and Panichayupakaranant 2016)

in natural field conditions. *Plumbago* species leaf, shoot tips, axillary buds, and internode are commonly utilized as explants in tissue culture methods (Beigmohamadi et al. 2021; Katoch et al. 2022). Through micropropagation, a single explant can produce many plantlets quickly and without getting affected by the environmental changes. *P. europaea* callus and cell suspension cultures were tested, and plumbagin was successfully produced using callus cultures and cell suspension cultures supplemented with 2,4-dichlorophenoxyacetic acid (2, 4-D) (1 mg l^{-1}) and Kin (0.5 mg l^{-1}). A dark-incubated culture contained more plumbagin than a photoperiod-incubated culture (Beigmohamadi et al. 2019). In vitro rooting of *P. zeylanica* was induced by 0.25 mg dm^{-3} indole-3-butyric acid on ½ basal MS medium (Saxena et al. 2000). Figures 5a, b, and c represent *P. zeylanica* growing in vitro, whereas Figs. 5d and e show HPTLC chromatograms and overlay spectra of several *P. zeylanica* samples, respectively, and Fig. 5f displays bands for plumbagin on a TLC plate.

Role of endophytes for the production of plumbagin

Plant microbiomes are dominated by endophytic fungi. Their symbiotic relationships with medicinal plants enable them to synthesize secondary metabolites in vivo. In the roots of *P. zeylanica*, Andhale et al. (2009) found three fungal endophytes (*Rhizopus* sp., *Aspergillus phoenicis*, and *Alternaria* sp.). These fungal endophytes increased plumbagin content substantially, with *Alternaria* sp. showing the greatest increase (122.67%) in the roots of *P. zeylanica* compared to control (Andhale et al. 2009). In spite of the fact that there are several ways available for improving plant secondary metabolites, microorganisms seem to be the most practical approach. According to Maggini et al. (2017), endophytes effectively increase the levels of secondary metabolites among microbes.

Conventional methods for propagation of *Plumbago* species

Conventional methods include general or basic methods used to propagate or produce plants, such as callus culturing, organogenesis (direct and indirect), embryogenesis (zygotic and somatic), and organ culture (Efferth 2019). Several in vitro research have demonstrated that in vitro grown plants/cultures accumulate more plumbagin than their in vivo counterparts. In a study conducted by Satheeshkumar and Seeni (2002), it was found that cell suspension culture produces plumbagin more efficiently than callus culture. For ex situ conservation and easy dissemination, polybags

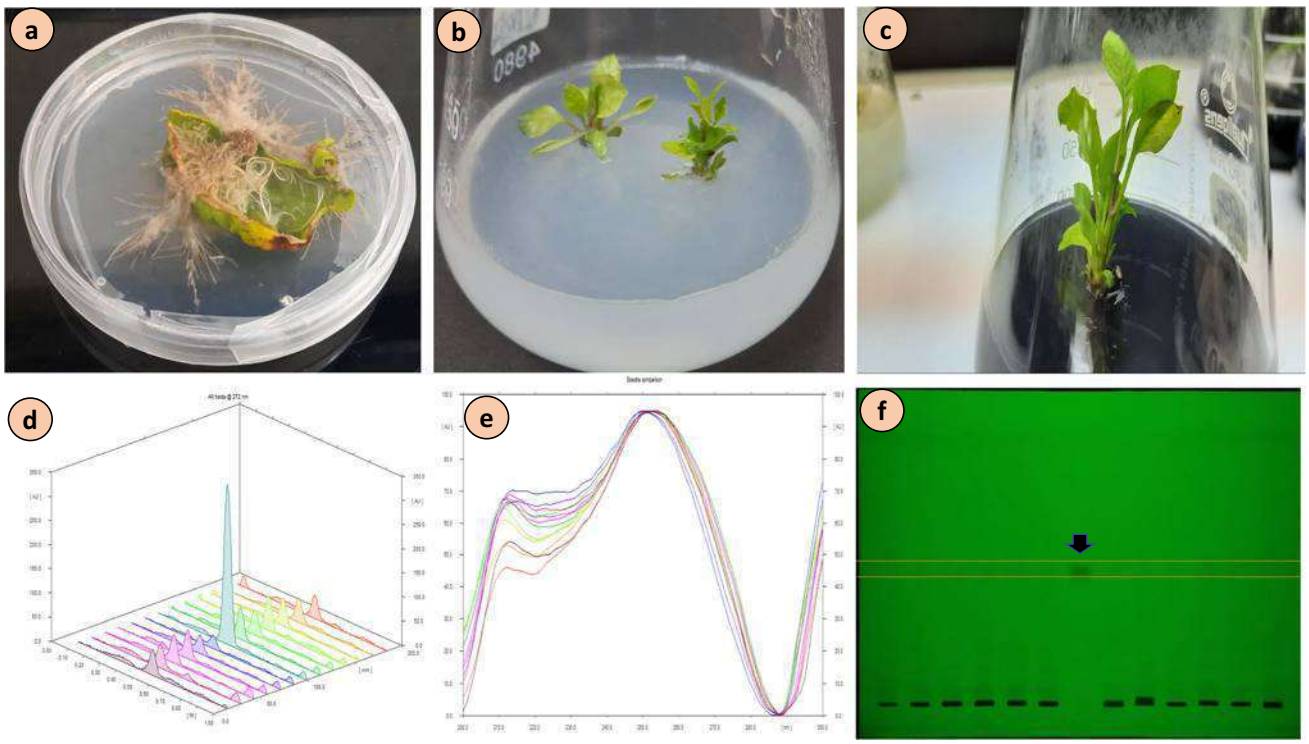

Fig. 5 **a** In vitro root multiplication. **b**, **c** In vitro shoot multiplication. **d** HPTLC chromatogram of different samples of *Plumbago zeylanica*. **e** Overlay of samples with standard plumbagin. **f** TLC plate showing bands for plumbagin

filled with soil, sand, and manure were used to multiply *P. zeylanica* (Patel 2015).

Micropropagation studies on *Plumbago* species

Nitsch and Nitsch conducted the first tissue culture studies on *P. rosea* in 1967 using internodal explants to induce callus, roots, shoots, and inflorescence/flower. In the same year, Nitsch and Nitsch (1967) induced shoot buds from internodal segments with a combination of adenine with various cytokinins, which was later substantiated by Handique and Chetia (2000). Das and Rout (2002) developed a methodology for regenerating plants using aseptic leaf explants generated in vitro. Satheeshkumar and Seeni (2002) reported on indirect organogenesis-based in vitro plant regeneration and how it affected field crop performance and early tuberous root harvest. Gopalakrishnan et al. (2009) developed micro shoots on leaf explants from *Plumbago* plants that had been cultivated in the field. Jose and Satheeshkumar (2010) developed a high-frequency regeneration strategy for plants from the tuberous roots of the field-grown *P. rosea*. Additionally, reports on plant regeneration using somatic embryogenesis and leaf explants without callus are available (Borpuzari and Borthakur 2016). The shoot organogenesis of *P. europaea* was studied in connection to explant type and plant growth regulators. Beigmohamadi et al. (2021) reported that MS media with 0.5 mg/l TDZ (11.62 shoots per node) was the best medium for proliferating nodal explants.

Indirect organogenesis or callus culture

In-direct organogenesis is the development of callus prior to the formation of shoots or roots, and the organs can be regenerated from the callus by supplying the optimum concentration of plant growth regulators. Lubaina and Murugan (2012) investigated the effect of growth regulators on the growth and plumbagin content of *P. zeylanica*. Surface sterilized leaf and stem explants were inoculated in MS media with 3% sucrose gelled and 0.8% agar. The cultures were incubated for 16 h under 3000 lx of white light, followed by 8 h of darkness, at room temperature (25–27 °C). A Combination of 2,4-D (1 mg/l) and BA (0.5 mg/l) was found to be best suited for callus induction, whereas for shoot regeneration, media supplemented with BA (1 mg/l) produced the highest number of shoots. The amount of plumbagin produced in vitro has also been found to be higher than the amount produced by plants grown in vivo.

Direct organogenesis

Direct organogenesis, which is the direct regeneration of organs from explants, is considered to be an effective technique for quickly creating a large number of plantlets. Das and Rout (2002) achieved direct shoot induction from *P. zeylanica* and *P. rosea* leaf explants with a 90% survival rate of the generated plantlets. For the best shoot proliferation, explants were inoculated in MS media supplemented with 1.5 mg/l BAP, 0.75 mg/l indole-3-butyric acid (IBA), 0.75 mg/l adenine sulfate, and 10% coconut milk for optimal shoot proliferation. Microshoots were grown in half-strength MS media supplemented with 0.75 mg/l IBA. The rooting response and survival rate of in vitro-generated plantlets in the natural environment were both determined to be 100%. On MS basal medium containing BAP (2.0 mg/l), IAA (1.5 mg/l), and IBA (1.0 mg/l), *P. zeylanica* showed 95% shoot proliferation from the nodal explants. Microshoots were grown in MS medium supplemented with α-naphthaleneacetic acid (NAA) (1.5 mg/l), IAA (1.5 mg/l), and IBA (2.0 mg/l). When transplanted to field conditions, the regenerated plantlets survived 100% of the time (Kanungo et. al. 2012) (Table 1). However, ¼ MS medium without any plant growth regulator was found to be optimal for rooting and shooting in *Drosera intermedia* R.Cunn. ex A.Cunn., another known plumbagin-producing species (Grevenstuk et al. 2010).

Culture systems for the production of plumbagin non-transformed cultures

Callus culture system designed for the production of plumbagin in *P. zyelanica* was first described by Heble et al. (1974). Nitsch and Nitsch (1967) was the first team to induce callus tissues from *P. rosea* flower and intermodal sections. Accordingly, several researchers generated callus tissues in *P. rosea* to produce plumbagin (Komaraiah et al. 2001; Satheeshkumar and Seeni 2002; Silja et al. 2014). Because of their greater ability to grow in submerged cultures, cell suspension cultures have a more direct potential for industrial use than organ cultures. From the late 1950s to the early 1960s, tobacco and other plant cells were scaled up and studied, sparking greater research into the industrial application of plant cell suspension.

Following the development of callus culture, various researchers established cell suspension cultures from callus tissues in order to produce plumbagin in *P. rosea* (Komaraiah et al. 2001; Satheeshkumar and Seeni 2002). Numerous cultural and physical parameters were improved to increase plumbagin production. Komaraiah et al. (2003) presented their findings on the effect of plant hormones on

Table 1 Selective protocols for callus culture of *Plumbago species*

Species	Explant	Culture	MS + PGR			References
			Callus induction	Shooting	Rooting	
P. rosea	Stem	Callus culture	MS + 2.5 mg/l 2,4-D + 1.5 mg/l kinetin + 3% sucrose	MS + 2.0 mg/l BAP + 1.0 mg/l NAA + 3% sucrose	MS + 1.5 mg/l IBA + 3% sucrose	Kumar and Bhavanadan 1988
	Leaves	Callus culture	MS + 1 mg/l IAA + 0.5 mg/l NAA + 0.3 mg/l BAP + 3% sucrose	-	-	Komaraiah et al. 2001
P. zeylanica	Leaves, stem	Callus culture	MS basal medium + 3% sucrose + 11.42 uM IAA + 2.22 uM BA (better callus from leaf explant)	MS basal medium + 3% sucrose + 4.44 uM BA + 1.42 uM IAA (better shoot induction from leaf explant)	½ strength MS + 0.57 uM IAA + 2% sucrose	Rout et al. 1999
	Stem	Callus	MS media + BAP (2.0 mg/L) + IAA (1.5 mg/L)	-	-	Sivanesan and Jeong 2009

plumbagin accumulation and the selection of stable cell lines.

Plumbagin production in *P. rosea* embryogenic cell suspension cultures was also shown to be greater than in non-embryogenic cultures (Komaraiah et al. 2004). Embryogenic cell suspension cultures with rapid growth and higher plumbagin production were later identified by Silja et al. (2014). Several methods for production plumbagin in *P. rosea* have been reported including media component optimization, single-cloning of cell lines, elicitation, permeabilization, immobilization, in situ product extraction, and cell cultivation in modified bioreactors, with a 20–25 times increase in plumbagin production (Silja et al. 2014).

Satheeshkumar and Seeni (2002) published the first report on establishing adventitious root cultures of *P. rosea* for the production of plumbagin. Later, it was reported that root cultures could be grown using young leaf segment (Silja and Satheeshkumar 2015). Induction and establishment of adventitious root cultures from cell aggregates of cell suspension cultures have also been reported (Silja et al. 2016). Apart from *Plumbago* spp, several other species such as *Drosophyllum*, *Drosera*, and *Nepenthes* have been utilized for the production of plumbagin under in vitro conditions. Though, several earlier studies have reported the influence of carbon source on the production of secondary metabolite compounds. Earlier workers have reported that manipulation of the culture environment influences the product accumulation. Exogenous phytohormones were studied for their effect on growth and plumbagin accumulation in *P. rosea* hairy root cultures. The significance of gibberellic acid on root growth and naphathalene acetic acid on plumbagin yield was established (Gangopadhyay et al. 2011a, b). Plant growth regulators have also been shown to have an effect on callus cultures, cell suspension cultures, and adventitious root cultures (Silja and Satheeshkumar 2015; Silja et al. 2016).

Contemporary or advanced method

Contemporary methods are advanced experimental approaches which involve the use of elicitors (biotic and abiotic), synthetic seeds, genetic manipulation, hairy root culture, bioreactors, metabolic engineering, use of endophytes, etc. The advent of these sophisticated propagation technologies enables growers to get preferred plant features. Several plants that produce pharmaceutically important secondary metabolites possess very little phytometabolite yield for commercial or industrial use (Table 2). As a result, the disadvantages of traditional in vitro culturing include lower productivity, cell line instability, and variance in metabolite output. Several biotechnological strategies have been used to increase the yield of plumbagin from a variety of plant species.

Elicitation The plant defense system is triggered by a number of chemical compounds, microorganisms, and physical stresses. This process is known as elicitation, and these compounds or factors are called elicitors. Recently, researchers have concentrated on implementing elicitors to produce plumbagin. It was found that *Azospirillum* enhanced plumbagin concentration in roots (0.027% w/w) in comparison to the control when chemical fertilizers and natural fertilizers were applied to *P. zeylanica* cultures (Patel et al. 2016). Silja and Satheeshkumar (2015) were able to develop adventitious roots of *P. rosea* that were swiftly growing and high yielding by improving the culture

Table 2 Direct organogenesis studies in *Plumbago species*

Species	Explant	Culture	MS + PGR		References
			Shooting	Rooting	
P. rosea	Leaves	Shoot	Shoot induction-MS + 6.66 uM BAP + 2.69 uM NAA Shoot elongation – 1.11 uM BAP + 1.44 uM GA_3	½ strength MS	Gopalakrishnan et al. 2009
	Internodes	Cell suspension culture	-	1.5 mg/l^{-1} NAA 1.0 mg/l^{-1} IAA	Silja et al. 2016
P. auriculata	Leaves, node, apical shoots	Root		MS media 1.5 mg/l IBA IAA and NAA 1.5 mg/l and 0.1 mg/l	Deshpande et al. 2015
P. zeylanica	Node	Bud	MS + 3% sucrose + 27.2 uM $AdSO_4$ + 2.46 uM IBA	MS + 4.92 uM IBA	Selvakumar et al. 2001
		Organ	0.44 µM BAP	Half MS media and 125 mg/l activated charcoal	Vijay et al. 2016
		Shoot	2.0 mg/l BAP + 0.2 mg/l NAA	1.0 mg/l IBA	Chatterjee and Ghosh 2015

conditions for root induction and growth with the use of different elicitor concentrations (jasmonic acid, yeast extract, and sodium salicylate). Over the course of 3 days, 50 µM jasmonic acid significantly increased the plumbagin concentration in roots to 1.23% DW. Silja et al. (2014) demonstrated in their preliminary investigation the enhancement of plumbagin synthesis by elicitation with jasmonic acid, yeast extract, and various auxin combinations in embryogenic cell suspension cultures of *P. rosea* leaf explants. After 6 days of incubation, cultures supplemented with 1 mg l^{-1} naphthalene acetic acid showed a 5.59-fold increase in plumbagin synthesis. With higher elicitor concentrations and longer incubation times, colonies' viability declined. To induce callus in *P. zeylanica*, Sharma et al. used NAA, IBA, 2,4-D, 6-benzyladenine (BA), isopentenyl adenine (2iP), or thidiazuron (TDZ) as supplements and yeast extract and salicylic acid as elicitors. The maximum number of roots observed on 5 µM IBA was 4.3 ± 1.36, and their average length was 15.31 ± 2.76 cm. Plumbagin content in root callus was significantly increased by using 100 mg l^{-1} yeast extract (YE) and 25 µM salicylic acid (SA) (6.5- and 3.4-fold, respectively) (Sharma and Agrawal 2018).

Precursor feeding

Precursors are chemical substances that are employed in metabolic reactions to produce other substances. Precursor feeding has long been utilized for a time to increase the generation of secondary metabolites. Plumbagin synthesis was significantly increased to 22.4 mg g^{-1} dry weight by the in situ adsorption of precursors such L-alanine (5 mM to 14 days old root culture (Jaisi and Panichayupakaranant 2017).

Agrobacterium-mediated gene transformation

Genetic engineering is the process of introducing a foreign gene (introduced gene) into a plant cell and causing that foreign gene to exhibit specific traits in the reproduced plant, thus modifying the original genetic makeup (Table 3). The significance of this technique lies in the considerable overproduction of the secondary metabolites (Sweetlove et al. 2017). *Agrobacterium*-mediated gene transfer has been reported in the literature on in vitro plumbagin production, making way for new techniques/experimental setups for sustainable plumbagin production.

The hairy root cultures of transformed plants accumulated more plumbagin than non-transformed roots. *A. rizogenes* was injected into internodes and leaf midribs and co-cultivated for 5–6 days in the experimental setup. The transformation of the roots was proved by PCR amplification via using suitable primers. A4-transformed rhizoclone HRA2B5 had the highest plumbagin concentration of 2.26 mg/g DW (Nayak et al. 2015). In a recent study, *A. rhizoigenes*-mediated transformation efficiency, co-cultivation time, and acetosyringone concentration were optimized to demonstrate the establishment of *P. europaea* hairy root cultures for the production of plumbagin. To achieve the highest transformation rate of 69.3%, a rhizogenes MSU440 strain was inoculated into 3-week-old stem explants after 7–9 days, followed by a co-cultivation phase of 2 days on medium containing acetosyringone (Beigmohamadi et al. 2020). Hairy roots are genetically modified roots that grow rapidly, plagiotropically, and are highly branched on phytohormone-free medium. *P. rosea* hairy root culture was first established by Gangopadhyay et al.

Table 3 Effect of various elicitors used *in vitro* culture to enhance plumbagin production

Species	Explant	Growth regulator	Elicitors	Achievements	References
P. rosea	Leaf	IAA, NAA, BAP	Fungi (*Aspergillus niger* and *Rhizopus oryzae*), bacteria (*Bacillus subtilis* and *Pseudomonas aeruginosa*), yeast extract and chitosan	Plumbagin production Chitosan treated cells 6.71-fold higher	Komaraiah et al. 2002
	Leaf-derived cell culture	IAA, NAA, BAP	Synergetic effect of chitosan, immobilization, and in situ extraction	Plumbagin yield:- 92.13 mg g^{-1} DCW	Komaraiah et al. 2003
	Leaf	NAA, BAP	Acetylsalicylic acid, ammonium	Plumbagin accumulation was 3 fold embryogenic compared to non-embryogenic suspensions	Komaraiah et al. 2004
	Node	BAP, NAA, 2,4-D	Jasmonic acid, yeast extract, NAA	Embryogenic cell suspension cultures treated with NAA increased plumbagin production by 5.59 fold compared to control plant	Silja et al. 2014
	Node	IAA, IBA, NAA	Jasmonic acid, sodium salicylate, yeast extract	Increased plumbagin content increased by addition of jasmonic acid to 1.23% DW	Silja and Satheeshkumar 2015
Drosera burmanii	In vitro cultured stem segments	BA	Methyl jasmonate, yeast extract, chitosan, or salicylic acid	Yeast extract increased plumbagin production by 3.5 fold than control plant	Putalun et al. 2010
Drocera indica	Seeds	Giberellic acid	Yeast extract, methyl jasmonate, chitosan, salicylic acid	Yeast extract (0.5 mg/ml) enhanced plumbagin by 5.4 fold compared to control plant	Thaweesak et al. 2011
P. indica	Leaf	NAA	Gamma rays	20 Gy dose of gamma ray increased the plumbagin production to 1.04 mg/g DW	Jaisi et al. 2013

(2008) in the Medicinal Plant Laboratory, Bose Institute, Kolkata, India. *A. rhizogenes* strain (ATCC 15834, A4 and LBA 9402) has been used to induce and establish transformed hairy root cultures of *P. rosea* for the production of plumbagin (Gangopadhyay et al. 2010; Pillai et al. 2015). As well as optimizing inoculum density in shake flasks and airlift bioreactors, Pillai et al. (2015) have attempted to enhance plumbagin production as well as root biomass.

Bioreactors scaling up of cultures

A bioreactor is referred to as an airlift bioreactor if the culture medium is stirred and aerated by the addition of air or another gas mixture. Hairy roots induced from *P. rosea* have been scaled up by Pillai et al. (2015) in a 2-l volume airlift bioreactor for plumbagin production. The number of reports about scaling up root cultures is very low. Pillai et al. (2015) scaled up plumbagin production using hairy roots induced from *P. rosea* in a 2-l volume airlift bioreactor. Jose et al. (2016) designed one such bioreactor or reaction kettle which accumulated 1.5% DW of plumbagin and boosted hairy root biomass by 12 times.

Encapsulation

The transformed plants are stored in the form of synthetic seeds. The roots of *P. indica* were transformed by *rolB* gene and treated with different hormones. It was found that lower concentration of all phytohormones gave

optimum results. The elite root clones were encapsulated in sodium alginate (Gangopadhyay et al. 2011a, b).

Genetic diversity assessment of *Plumbago*

Genetic diversity is defined on the basis of polymorphism, i.e., the difference in the DNA sequence of a DNA segment (Table 4). Genetic integrity of the micropropagated *P. zeylanica* plants were assessed by RAPD profiles, and the micropropagated plants exhibited no polymorphisms (Rout and Das 2002). The characterization of germplasm is an essential form of identifying the elite genotypes as well as the variability of various population of *Plumbago*. It is the basis for the plant adaptation to its natural climate, evolution, and breeding for the plant improvement. These information lead to the development of superior varieties. The transformed plants are stored as synthetic seeds. The roots of *P. indica* were transformed by the *rolB* gene and treated with various hormones. It was discovered that a lower concentration of all phytohormones gave the best results, and the elite root clones were encapsulated in sodium alginate (Gangopadhyay et al. 2011a, b).

Table 4 Enhanced plumbagin production following *Agrobacterium*-mediated transformation

Species	Explant	Plant growth regulators	Strain	Results	References
P. zeylanica	Leaves	BAP, IBA	*A. rhizogenes* strain A4	Rooting 0.49 mmol/L IBA (1/2 strength medium) Shooting 8.87 mmol/L BAP and 0.49 mmol/L IBA 2.5 times higher amounts of plumbagin	Verma et al. 2002
	Cotyledon, hypocotyl and petiole	BA, ZT, AD,2,4D, IAA, IBA,NAA, CM	*A. tumefaciens* strains AGL1 and LBA4404	Rooting ½ strength MS medium with 0.1 mg/l IBA Shooting Petiole-1.5 mg/l BA + 0.25 mg/l IAA + 50 mg/l AD + 10% CM Leaf strip-1.5 mg/l BA + 0.25 mg/l IAA + 50 mg/l AD + 10% CM	Wei et. al. 2006
P. indica	Hairy root	-	*A. rhizogenes* strain ATCC 15834 pH 5.6 and 3% sucrose	Highest plumbagin content in roots at exponential phase of growth	Gangopadhyay et al. 2008
	Hairy root	IAA, BA	*A. rhizogenes* strain ATCC 15834	Higher root bio-biomass and an increased plumbagin content compared to non-transformed plants	Gangopadhyay et al. 2010
	Hairy root	IAA, IBA, 2, 4-D, NAA, BAP, GA3, ABA	*A. rhizogenes* strain ATCC 15834	Root growth 0.5 mg l^{-1} GA3 Plumbagin accumulation 0.5mgl − 1 NAA Root biomass and plumbagin production GA3 + NAA (0.5 mg l^{-1}, each)	Gangopadhyay et al. (2011a)
	Leaf and internode explants	BA, IBA	*A. rhizogenes* strain A4M70GUS elicitation by methyl jasmonate, acetylsalicylic acid	50 µM methyl jasmonate for 48 h increased the yield of plumbagin to 5.0% dry weight	Martin et. al. 2011

Phytochemical markers

The generation of bioactive molecules is influenced by a number of variables. Information regarding the best accessions is provided via the biochemical study of several accessions. Several researchers have attempted to search the literature for phytochemical variation studies on *Plumbago* species (Roy et al. 2022; Cheemalapati et al. 2022; Liu et al. 2022; Purwoko et al. 2022; Ajayi Gabriel et al. 2019; Rajakrishnan et al. 2017). *P. indica* and *P. auriculata* hydroalcoholic extracts were analyzed by LC–MS/MS to identify thirty and twenty-five compounds, respectively. Both extracts contained 21 compounds in common. Based on retention times, molecular weights, and fragmentation patterns, compounds were identified and tentatively annotated (Selim et al. 2022). Using light microscopy, Galal et al. (2013) compared the anatomical features of *P. auriculata*, *P. indica*, and *P. zeylanica* leaves, stems, and roots. GC–MS analysis of aerial part *P. zeylanica* extracts identified 1,4-naphthalenedione, 3-eicosene, 5-eicosene, phthalic acid, *o*-anisic acid, thioctic acid, 1-octadecene, 5-*t*-butylcycloheptene, 2-benzoyl-1,2-dihydro-1-isoquinolinecarbonitrile, octadecanal, silane, 3-methoxy-2-methyl-2-(1-phenylethylamino)-propionic acid, and 1-nonadecene (Roy et al. 2022). Heneicosane is also isolated from ethyl acetate leaf extracts of *P. zeylanica* (Vanitha et al. 2020). Dissanayake et al. (2022) also screened *P. indica* root bark via GC–MS and detected plumbagin. Tripathi et al. (2022) recently reported 2,6-di-tert-butyl phenol and 2,4-di-tert-butyl phenol from *P. indica*.

Conclusion and future prospects

Until now, an impressive literature on pharmacological investigation breakthroughs in plumbagin production has been published (Beyene et al. 2020; Jenifer et al. 2021). The various pharmacological activities of plumbagin have been widely documented over the last decades, and the synergetic effect on various cancer cells and microorganisms suggests that that further research should be conducted in order to improve plumbagin accumulation, yield, and smart harvest. Plumbagin is primarily present in roots, which necessitates a destructive harvest and the loss of whole cultivation. To address these issues, other biotechnological options must be investigated. In vitro culture is a critical and secure method for producing plumbagin. Elicitation is another approach for increasing plumbagin content in the *Plumbago* species during in vitro cultivation. The biosynthetic pathway is poorly understood, which might be a hurdle at times, so the pathway must be adequately described to facilitate medication discovery using plumbagin as a natural template. More research on genetic diversity evaluation using molecular markers should be conducted in order to identify and validate high-producing species.

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Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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Genetic diversity assessment and biotechnological aspects in Aristolochia spp

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MINI-REVIEW

Genetic diversity assessment and biotechnological aspects in *Aristolochia* spp.

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Abstract

Aristolochia, belonging to the family *Aristolochiaceae*, has immense ecological significance due to its large size and huge geographic distribution. In the context of dealing with a genus with a huge number of species like *Aristolochia*, these markers come in handy to precisely identify a particular species and enumerate the genetic diversity. Also, certain species of *Aristolochia* are economically important due to the presence of secondary metabolites and vast use in traditional and modern medicine. But, the presence of profitable biochemical constituents in *Aristolochia* is very low and the breeding process of the plant is highly dependable on pollinators. Hence, identifying different biotechnological approaches to fasten the reproductive cycle of *Aristolochia* and increase the secondary metabolites is of great interest to the researchers. In this study, a comprehensive review has been established on different types of morphological/anatomical markers (starch grains with "Maltese cross"), phytochemical markers (aristolochic acid, triterpenoid, aristolactam etc.) and genetic markers (ISSR, SSR, DNA bar-coding) for various *Aristolochia* spp. We have also discussed the applications of different biotechnological tools in *Aristolochia* spp. which include discrete approaches to promote in vitro germination, in vitro shooting, root induction, somatic embryogenesis, synthetic seed production, acclimatization and hardening and sustainable production of secondary metabolites. In a nutshell, the present review is a first of kind approach to comprehensively demonstrate the genetic diversity studies and biotechnological aspects in *Aristolochia* spp.

Key points

- *Insights into the* in vitro *propagation of Aristolochia spp.*
- *In vitro production and optimization of secondary metabolites.*
- *Assessment of genetic diversity by molecular markers.*

Keywords *Aristolochia* · ISSR · DNA barcoding · Aristolochic acid · In vitro culture · Synthetic seed

Introduction

Aristolochia is a large genus of flowering plants having a large geographical distribution almost all over the world in various diverse climatic situations. The members are often called birthwort, due to the resemblance of the flower with the birth cannel (Ansari et al. 2021; Qin et al. 2021).

Aristolochia is considered to be toxic due to the presence of aristolochic acids (AAs) which causes chronic renal failure, urothelial malignancies and tubulointerstitial fibrosis together termed as aristolochic acid nephropathy (AAN) in both humans and mice (Jelaković et al. 2019 Ji et al. 2021). Consumption of food containing AA through traditional medicine or ingestion of food that is environmentally contaminated with AA can cause progressive renal interstitial fibrosis that frequently leads to AAN. AA intoxication leads to haemodynamic abnormalities by causing an increase in endothelin and reduction in renal nitric oxide levels. Due to such an imbalance in vasoactive factors, vasoconstriction happens to lead to hypoxia, tubular injury, inflammation and ultimately fibrosis.

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However, *Aristolochia* have widespread use in various regions. Like in Europe, *Aristolochia* sp. were introduced by the Greek scholar Dioscorides (first century), and aristolochic acid and its extracts isolated from *Aristolochia clematitis* were formerly approved to treat against eczemas, abscesses and different long-lasting dermatosis and as a stimulant for immune system (Scarborough and Fernandes 2011; Pohodina et al. 2019). The whole plant of *Aristolochia* is considered to hold different types of medicinal properties in Indian traditional medicine. The roots of *Aristolochia* are designated as anti-inflammatory, diuretic and cardiotonic due to the presence of an alkaloid, aristolochin; leaves are useful for the treatment of cholera and intermittent fever in children; and seeds are traditionally used against inflammation, biliousness and dry cough (Padhy 2021). Hence, a throughout heath risk assessment should be done before using this kind of drugs for any medicinal practices.

On the other hand, various species of *Aristolochia* (viz. *A. longa, A. triangularis, A. bodamae, A. longa* etc.). and their compounds have been reported to demonstrate profound antimicrobial properties (Pereira et al. 2018; Dalcol et al. 2021; El Omari et al. 2020; Ozen et al. 2020; Doudach et al. 2022). Therefore, in vitro cultures can be used as an exciting option to produce and characterize the antimicrobial phyto-constituents from the plant. Besides the genus is also known to host many endophytic microbes (Guevara-Araya et al. 2020, 2022) which can also be cultured in vitro for the production of secondary metabolites. Aristolochic acid (AA) has the potential inhibitory role against snake venom L-amino acid oxidase (LAAO). As AA is notorious for its genotoxic activity, its non-toxic artificial hydroxyl and chloroderivatives can be used for such purpose (Bhattacharjee et al. 2017).Improvements in in vitro techniques offer novel strategies to the viable processing of even threatened and endangered plants and their economically and industrially promising secondary metabolites. In vitro propagation of medico-botanicals and in vitro optimization of their bioactive principles have been done in many plants for the commercial production of therapeutically active plant-based medicines. In plant tissue culture, the production of secondary metabolites has been reported from various species (Jayaprakash et al. 2021; Manokari et al. 2021; Shekhawat et al. 2021; Swamy et al. 2021). Many reports involve the use of different elicitors to increase the quantity of plant secondary metabolites (Dey et al. 2019, 2020; Nandy et al. 2021; Pandey et al. 2021; Nazir et al. 2021a). The present review encompasses an outline on the in vitro propagation and biotechnological tools as an aid for clonal propagation and production of aristolochic acid and allied compounds. In addition, for its use as multipurpose drug in traditional and modern medicines and presence of important toxins, tissue culture *Aristolochia* is a better way out for faster growth, low dependence on natural pollinators and to conserve its short genotype. *Aristolochia* is exploited as a model plant for in vitro regeneration and formation of artificial seed (Remya et al. 2013), clonal propagation (Sarma and Tanti 2017b) and somatic hybridization (Bliss et al. 2009).

A study of markers not only help to distinguish between different population and individual plant itself but also provide insights into the different genetic arrangement, phytochemical constitutes and morphological parameters of one group of plants (Kaur et al. 2019; 2021; Nazir et al. 2021b; Tikendra et al. 2021a,b). Different types of morphological, phytological and genetic markers of *Aristolochia* is well established to differentiate the species of this large genus. Also such markers can be useful as a genetic and breeding tool for crop development (Chesnokov et al. 2020; Desai and Tatke 2019). Therefore, methodologies for measuring genetic diversity and/or proximity in different species utilizing various markers have also been elucidated (Table 1).

Distribution

Aristolochia spp. is a genus present in the family of *Aristolochiaceae* which include approximately 550 species (Cai et al. 2020). All these species are distributed generally under tropic, subtropic, Mediterranean and temperate regions of the world including America, Asia and Africa (Fig. 1). *Aristolochia* subgenus *Siphisia* include 70 species in which 50 of them are found in the southern and eastern parts of Asia, while 20 of them are found in the central and northern parts of America (Do et al. 2015). *Aristolochia ringens* species is found in the tropical regions of America and Africa, whereas *Aristolochia elegans* species are native for South America, while it is exotic for North America, Africa and Asia. Vietnam's tropical, humid and forest region favour the growth of species like *Aristolochia bidoupensis* (van Do et al. 2016). *Aristolochia delavayi*is widely distributed in southwest China along with the Jinsha river valley at an altitude of 1220–2250 m (Yu et al. 2021). In India, 18 species of the genus *Aristolochia* is found, in which *Aristolochia maxima* is found in north Western Ghats (Tilari Ghats) of Maharashtra (Pandurangan and Deepu 2018). This species is native for central and South America. Another species *Aristolochia indica* is found throughout tropical, subtropical and Mediterranean countries including India, Nepal and Bangladesh (Dey and De 2011; Sarma et al. 2018). In Africa, generally on the western side, Madagascar favours the growth of 11 species which include *A. albida*, *A. baetica*, *A. bracteolate*, *A. embergeri*, *A. heppi*, *A. hockii*, *A. fontanesii*, *A. paucinervis*, *A. pistolochia*, *A. rigida* and *A. sempervirens* (de Groot et al. 2006). There are three medicinal and endemic *Aristolochia* species from eastern India

Table 1 Different types of markers found in *Aristolochia* species and populations

Markers	Result/responses	References
Morphological markers	Investigated the root anatomy of *A. indica* by pharmacognostic profiling	Sudhakaran (2014)
	Found separated secondary xylem	
	Found thin-walled cork cells, small cortex and inner cortical cells interspersed with groups of stone cells	
	Found deposited starch in parenchymatous cell of medullary rays	
Phytochemical markers	Analysed the *A. baetica* for the phytochemicals markers like polyphenol, alkaloids, flavonoids, saponins and tannins	Bourhia et al. (2019)
	In *A. bracteolata* alkaloids, glycosides, saponins, starch and protein were analysed. Aristololochic acid and triterpenoid as distinctive phytochemical markers were seen	Avchar (2021)
	Eight aristololactams and 5 aristolochic acid derivatives were reported in *A. moupinensis*, and 6 aristololactams and 3 aristolochic acids were reported in *A. cathcartii*	Zhang et al. (2016)
	Eight aristololactam-type alkaloids and 7 aristolochic acid derivatives were found in *A. tagala*	Liu and Zhang (2020)
	Found 75 essential oil compounds in 10 *Aristolochia* species which classify the species into 4 morphological groups based on principal component analysis	Francisco et al (2008)
	Twenty accessions of *A. indica* were assessed for aristolochic acid content	Dey et al. (2021a, b)
(Molecular markers) ISSR	Evaluation of genetic diversity within 4 *Aristolochia* species *A. indica, A. cathcartii, A. saccate* and *A. tagala* by using 8 ISSR primers	Sarma and Tanti (2017b)
	Check the 9 out of 66 PCR amplicon's bands which are similar in terms of evolutionary history	
	Check the dendrogram of these 4 species for genetic diversity	
SSR	Evaluation of genetic diversity of *A. delavayi* in 193 individuals from ten different natural populations by using 15 pairs of microsatellites SSR primers	Yu et al. (2021)
	Analyse through AMOVA for genetic diversity among the population	
	Analyse the genetic diversity due to restriction of gene flow of *A. delavayi* population along with the Jinsha river	
DNA barcoding	Evaluation of polymorphism within 11 species of *Aristolochia* from Thailand by using *rbc*L, *mat*K, ITS2 and *trn*H-*psb*A as markers	Dechbumroong et al. (2018)

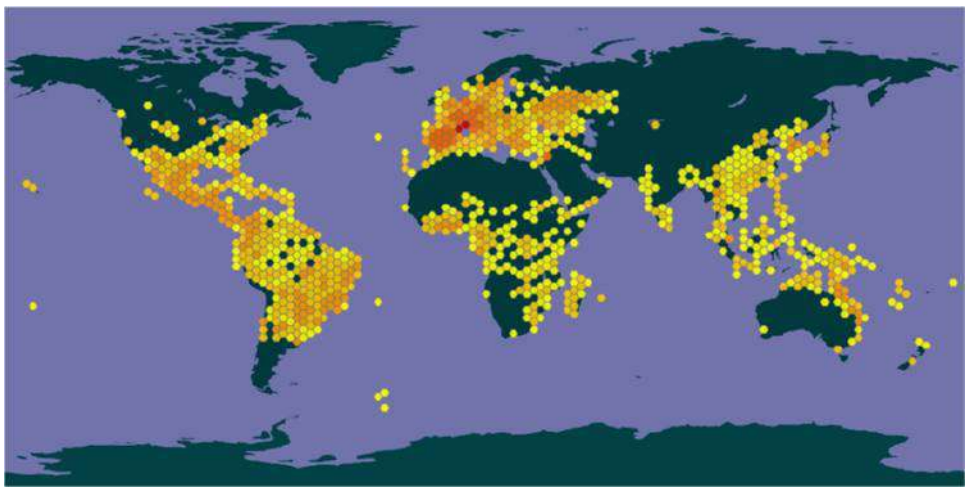

Fig. 1 Worldwide distribution of *Aristolochia* L. (source: https://www.gbif.org/species/2873978)

which have been reported namely *Aristolochia indica* Linn., *Aristolochia saccata* Wall. and *Aristolochia cathcartii* (Sarma and Tanti 2015). *Aristolochia delavayi*, another medicinal and endangered member of Aristolochiaceae, is endemic to China. They generally grow in the warm and dry areas along the Jinsha river (Yu et al., 2021).

Botanical description

Aristolochia is the type of genus of the family *Aristolochiaceae* or the birthwort family having over 450 species in 3 subgenera; *Aristolochia*, *Siphisia* and *Pararistolochia* (Wanke et al. 2006; Yan and Ma 2019). Among them *Aristolochia* itself has approximately 350 species. They are generally evergreen or deciduous lianes. But some deciduous herbaceous members from Mediterranean region are also investigated (Neinhuis et al. 2005). Leaves are found to be 3–7 lobbed, most of the time cordate, 3 (*Aristolochia dalyi*) — 7 nerved (Gonzalez 1998). In *Aristolochia longissima* and *Aristolochia ornithorhyncha*, conspicuous pellucid gland dots are present with the leaves (Jimenez et al. 2021). Flowers are irregular, either solitary or in groups and axillary in position. Perianth is colourful, tubular with various bending, generally flattened at the base but narrow near the throat and pubescent on the inner side; limbs can be either open or recurved, entire or lobbed. Stamens are 6 or more; anthers sessile adnate to the stigma or the back of style. Style is short and lobed near the apex with usually 6-locular inferior ovary. Fruit is capsule, and septicidally dehiscent; seeds are compressed (Britannica, T. Editors of Encyclopaedia, 2013).

In some instances, various authors showed their disagreement with these common morphological features of the different species of such vast genus like *Aristolochia*. Like, González and Stevenson had interpreted the perianth of *Aristolochia*as a trimerous calyx based on morphology, position, development and juxtaposition with the closely related taxa (González and Stevenson 2000) after studying 42 species.

Adams et al. have done a comparative study between 4 closely related species of *Aristolochia* from all over the world namely *A. californica*, endemic to California, *A. macrophylla* and *A. tomentosa* of eastern USA and *A. manshuriens* of eastern Asia based on seed characters (like seed mass, surface area wings, state and shape of embryo). It was found that though having similar morphological characteristics of the embryo (linear and underdeveloped), those features are statically different which assign them into 4 separate species (Adams et al. 2005).

Aristolochia was found to have a profound trapping mechanism for pollination in case of in proterogynous flowers. Experiments on 6 Mediterranean species have shown during female flowering stage an array of well-developed trichomes present on the underlying surface of the flower which ensure the entry of the pollinators into the flower but inhibit their exit. But after the flowers enter the stages of anthesis, the inner surface characters of the flower modify to enable the insect to escape (Oelschlägel et al. 2009).

Genetic diversity assessment

Morphological markers

Morphological markers are visual phenotypic characters of a plant that is particular to the certain species or genus. But the main disadvantage of these markers is that they are few in number and always influenced by environmental factors and covers of the entire genome (Chesnokov et al. 2020).

Sudhakaran has investigated the root anatomy of *Aristolochia indica* through pharmacognostic profiling and found the transverse section having a circular outline with tissue organization of thin-walled cork cells, small cortex and inner cortical cells interspersed with groups of stone cells. Secondary xylem was separated to form narrow strips. Wide medullary rays had greater quantities of parenchyma with ray cells having deposition of starch. Solitary vessels are occluded with tyloses and starch grains with 'Maltese cross'. He suggested these specific anatomical characters might be an authentic marker of this taxon (Sudhakaran 2014).

Phytochemical markers

Phytochemical markers are chemical constituents made up of single or group of herbal drugs with a well-defined chemical structure. These constituents may or may not possess any medicinal characteristics but are useful for quality control of plant-based drug or formulation (Desai and Tatke 2019). The genus contains a number of constituents which can be utilized as important phytochemical markers (Fig. 2).

Aristolochia baetica is a wild member of *Aristolochia* from Morocco whose roots have been used against cancer from a long time ago. The root aqueous extract of *A. baetica* was subjected to preliminary qualitative phytochemical screening to find out about the phyto-organic component behind their biological activities. The presence of polyphenol, alkaloids, flavonoids, saponins and tannins has been observed (Bourhia et al. 2019). Similar study also was done on the methanolic root extract of *A. bracteolata* which has also shown the presence of alkaloids, glycosides, saponins, starch and protein. High performance thin-layer chromatography fingerprinting study revealed the occurrence of aristololochic acid and triterpenoid as distinctive phytochemical markers of the particular plant (Avchar er al., 2021).

In a study to explore the phytochemical constituents of *Aristolochia moupinensis* and *Aristolochia cathcartii*, 8 aristolactams and 5 aristolochic acid derivatives were

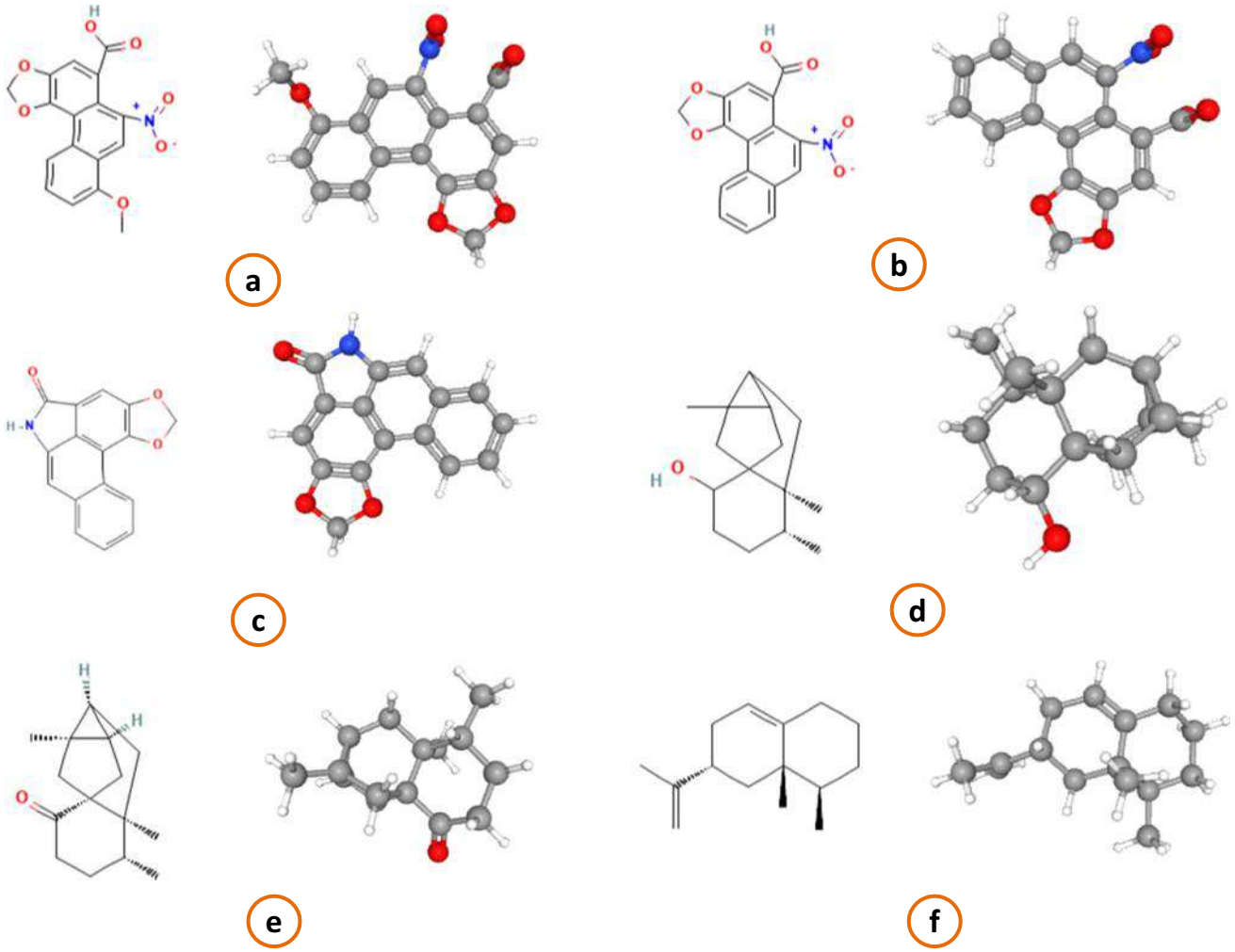

Fig. 2 2D and 3D chemical structures of the bioactive compounds of *Aristolochia* spp.: **a** Aristolochic acid I, **b** Aristolochic acid II, **c** Aristololactam II, **d** Ishwarol, **e** Ishwarone, **f** Aristolochene (source: www.PubChem.com)

isolated from *A. moupinensis*, whereas 6 aristolactams and 3 aristolochic acids were isolated from *A. cathcartii* (both were isolated from whole herb). Aristolactam I, aristolactam AII, aristolochic acid A and aristolochic acid BII were found from both of the species. Aristolactam-type alkaloids and aristolochic acid derivatives were widely spread in all the plant members of genus *Aristolochia*. Aristololactam is an intermediate in the biosynthetic pathway for aristolochic acid. The aristolochic acids in the *Aristolochia* possessed a unique chemical structure and are responsible for the same biological property of *Aristolochia* species. Hence, aristololactam-type alkaloids and aristolochic acids derivatives might be hypothesized to be unique for the particular genus, thus could be used as potential phytochemical markers for the genus (Zhang et al. 2016).

Eight aristololactam-type alkaloids and seven aristolochic acid derivatives were isolated from the whole plant of *A. tagala*. Among them sauristolactam and 7-methoxyaristololactam IV are very unique to the species. Sauristolactam is not found in any other *Aristolochia* species and though the occurrence of 7-methoxyaristololactam was observed in some of the Asian members of *Aristolochia*, it is quite rare. Hence, both of them could be used as chemotaxonomic or phytochemical marker of the species (Liu and Zhang 2020).

After analysing the essential oils from the roots of 10 *Aristolochia* species by GC–MS, 75 compounds were found. Multivariate analysis of those chemicals from roots classifies the 10 species into 4 morphological groups based on principal component analysis. The groups were identified by principal component 1 (monoterpenes, like a-thujene) and principal component 3 (sesquiterpenes, such as germacrene A (52), c-elemene (39) and b-gurjunene) (Francisco et al. 2008).

Group 1: A. arcuata, A. chamissonis, A. lagesiana, A. melastoma and A. pubescens.
Group 2: A. gigantean (highest positive PC1).
Group 3: A. elegans (highest positive PC3).
Group 4: A. esperanzae, A. galeata, and A. malmeana.

Molecular markers

ISSR

Inter-simple sequence repeats (ISSR) is a molecular technique which helps in the determination of multi-locus marker (repetitive sequence present in genome of organism) by the help of PCR by using microsatellite sequence as primers. The amplicons produced by this technique help in the study of evolutionary history, genetic diversity and gene mapping of closely related species. Forty-five Passion fruit (*Passiflora* sp.) accession was selected to check against eighteen ISSR primers. The result obtained from the mean Shannon–Weaver diversity index was 0.32 which represents a good diversity in the selected *Passiflora* germplasm by the ISSR markers (Santos et al. 2011). In another study, 23 mango germplasm accessions were collected from Guangxi province, China and checked against 18 ISSR primers. The result showed out of 156 bands, 87 are polymorphic. It can be concluded among the other cultivars, the genetic similarities in Xiang Ya mango type and their progenies are very high (Luo et al. 2011).

To determine the genetic variation of *Aristolochia s*pecies, 8 ISSR primers are used for the 4 species from Assam. These species are *A. indica*, *A. cathcartii*, *A. saccata* and *A. tagala*. It is found that *A. indica* and *A. cathcartii* (Cluster-I) are 62% similar in terms of genetic variation while *A. saccate* (Cluster-II) is 28% similar with Cluster-I species, while *A. tagala* (Cluster-III) is 22% similar with *A. saccate*. Nine out of 66 PCR amplicon's bands of these four species are similar indicating that they are sharing common evolutionary history. Remaining bands are the proof for the genetic divergence present in the species and showing polymorphism in their character. Dendrogram of these 4 species also shows the same genetic similarity for *A. indica* and *A. cathcartii*, while the other two species are not much closely related due to divergence in the genes (Sarma and Tanti 2017a).

SSR

Simple sequence repeat is a microsatellite DNA repeat found in genome having a high rate of polymorphism and widely distributed within the eukaryotic organisms, and the number of repeat is very specific and varies between organisms and helps in the assessment of genetic diversity between closely related organisms having minimal characteristic differences. Twenty-nine cucumbers (*Cucumis sativus* L.) accessions were selected to estimate the genetic diversity by comparing 13 genomic microsatellites (gSSR) and 16 expressed sequence tag (EST)-SSR (eSSR) markers. The dendrogram produced individually from the results of both of these markers shows similarity in the position of most of the cucumber germplasm. Comparing the data from eSSR markers, independent sub-clusters can be identified containing five germplasms. They all are resistant to downy mildew concluding a probable connection between those eSSR markers and disease resistance of plants (Hu et al. 2011).

SSR analysis is performed for the analysis of genetic diversity and difference in genetic makeup of the *Aristolochia delavayi* species with respect to its wild type. Fifteen pairs of microsatellite SSR primers are used for 193 individuals from ten natural populations. Through AMOVA (analysis of molecular variance), 68.4% genetic diversity is seen within the population, whereas 31.6% genetic diversity is seen among the population of *Aristolochia delavayi*. High genetic diversity within the population is due to outcrossing within the population by sexual reproduction or due to the retention of genetic resources. Restriction of gene flow may cause the less genetic diversity among the population which restricts the reproductive abilities of plants.

Since *Aristolochia delavayi* is found along the Jinsha River and warm and dry areas of China, so this kind of geographical habitat restricts the exchange of gene among the species. Another reason is that pollination of this species mainly depends on the family Ceratopogonidae and Chironomidae pollinator which are less efficient and have weak flying abilities and warm and dry climate does not favour the dispersal of seed due to which gene flow is restricted within the species and cause major genetic diversity within the population (Yu et al. 2021).

DNA barcoding DNA barcoding is the technique in which short sequence of DNA or organelle DNA is used to identify and help in the comparison of genetic diversities among species. The genes which are used as DNA barcode include cytochrome *c* oxidase I (COI or COX1) coding gene present within mitochondrial DNA, internal transcribed spacer (ITS) rRNA etc. due to their less variation in intraspecific level compared to interspecific level in species. Four plastid coding genes (rpoB, rpoC1, rbcL and matK) and 3 noncoding spacers (atpF-atpH, psbK-psbI and trnH-psbA) based on the chloroplast genome sequence of *Lemna minor* as proposed by the CBOL (Consortium for the Barcode of Life) were used to distinguish 97 accessions representing 31 species of Lemnaceae (aquatic monocots). It can be concluded that among other genes chosen in the study, the atpF-atpH noncoding spacer could be used as a universal DNA barcoding marker for species-level identification for Lemmaceae based on reliable amplification, straightforward sequence

alignment and rates of DNA variation between species and within species (Wang et al. 2010).

Recent studies on DNA barcoding use *rbc*L, *mat*K, ITS2 and *trn*H-*psb*A as markers to identify the genetic variability and polymorphism within the 11 species of *Aristolochia* from Thailand. This evaluates the highest variations which are found in ITS2 (28.98%) region of DNA followed by *rn*H-*psb*A (11.56%), *mat*K (11.15%) and *rbc*L (3.29%) in all 11 species of *Aristolochia* (Dechbumroong et al. 2018).

Achievements made in *Aristolochia* through modern biotechnological tools

In vitro germination

In vitro germination is an easier method to propagate for conservation and economic purposes (Table 2). The in vitro germination of *Cannabis sativa* seeds has faced some difficulties regarding uniformity and germination time due to issues in the standardization of disinfection procedures. A recent study has been mediated by using the generalized regression neural network (GRNN) to assess the type and concentration of disinfectants and the time of immersion for in vitro germination of the seeds. The results showed that treating the seeds with 4.6% sodium hypochlorite along with 0.008% hydrogen peroxide for 16.81 min manifested the best results with a 0% contamination rate and 100% germination after scarification within 1 week (Pepe et al. 2021).

The presence of scanty endosperm and linear, small embryo of *Aristolochia tagala* makes the germination of the seeds under normal conditions inconvenient (Biswas et al. 2007). Therefore, these factors have driven the utilization of different techniques of in vitro germination in order to enhance the viability of seeds and propagation rate. A report by Krishnan et al. (2019) suggested that exposure of seeds presoaked in warm water (50 °C) for 5 min to a germinator not only amplified the germination percentage but also successfully reduced the number of days taken for germination. The percentage of germination, however, was found to be greater in contrast to presoaked seeds exposed to an open room. According to Bhat et al. (2020), presoaking of seeds with warm water tends to stimulate the softening of seed coat and promotes rapid protrusion of tip of radicle upon attaining maturity. GA_3, KNO_3 and thiourea treatment at varying concentrations was found to have a pronounced effect on the rate of germination and effectively reducing the time taken for germination. Thiourea, a potential agent of in vitro germination, elevates endogenous cytokinin levels to alleviate inhibition on seed coat.

In vitro shooting

Morphogenesis from callus culture using a wide array of explants including adventitious shoot, nodes, internodes and leaves is beneficial for developing multiple clones of endangered medicinal plants. In vitro organogenesis can be manipulated by regulating the concentration of plant growth regulators (PGRs) specifically auxin and cytokinin. Though cytokinin along with auxin has a positive impact on shoot proliferation from callus, higher concentration of BAP (benzyl amino purine) and KIN (kinetin) can counteract this activity. It is also essential to utilize phloroglucinol to support in vitro shooting since accumulation of phenolic compounds may interfere with the normal phenomena and turn the callus black. In a study conducted on rice to standardize a reproducible and highly efficient plant regeneration protocol, the highest shoot regeneration was observed on the Murashige and Skoog (MS) medium supplemented with 2.0 mg/L benzylaminopurine, 0.5 mg/L 1-naphthaleneacetic acid, 500 mg/L proline and 500 mg/L glutamine in the callus obtained from MS medium complemented with 2.0 mg/L 2,4-dichlorophenoxyacetic acid (2,4-D), 500 mg/L proline and 500 mg/L glutamine (Pawar et al. 2015).

The most effective result of shoot organogenesis in *Aristolochia* from callus culture was recorded with BAP in combination with NAA. Media of 2 µM BAP, 1 µM NAA (1-naphthalene acetic acid) and 10 µM PG in MS (Murashige and Skoog) or MS media fortified with 2,4-D (2,4-dichlorophenoxyacetic acid) and KIN provided prominent results (Remya et al. 2013). The capability of NAA to initiate shoot organogenesis was put forward by Biswas et al. (2007), where 79% explants cultured showed successful shooting with 2 mg/L BAP and 0.5 mg/L NAA in *A. tagala*. In *A. saccarta* and *A. cathcartii,* 3–4 mg/L BAP and 0.5–1 mg/L NAA demonstrated the highest mean shoot length of 4.02–4.34 and the number of shoot in the range of 3.4–6.2 (Sarma and Tanti 2017a, b). Remya et al. (2016) suggested for elongation of shoot from apical bud explant, it is convenient to supplement MS media with GA_3. This report validated that BAP with KIN is even a fruitful alternative for in vitro shoot formation along with 0.1% charcoal fortification. BAP and spermidine, a polyamine, synergistically assisted the proliferation of shoot from nodal explant-derived calli (Dey et al. 2020).

Root induction

Root organogenesis from a wide variety of explants under precisely suitable culture conditions are dependent upon the type and concentration of auxin present in the medium. Germplasm conservation and reduplication *Artemisia* sp. for research and therapeutic purposes through biotechnological interventions have been greatly studied for the past decade.

Table 2 Different types of in vitro culture achieved in *Aristolochia* via tissue culture

In vitro culture type	Plant	Result	Reference
In vitro germination	Seeds of *A. tagala*	Exposure of seeds presoaked in warm water (50 °C) for 5 min amplified the germination percentage and reduced the germination time	Krishnan et al. (2019)
	Seeds of *A. tagala*	Presoaking the seeds with warm water stimulate the softening of seed coat and promotes rapid protrusion of tip of radicle during maturity	Bhat et al. (2020)
In vitro shooting	*A. tagala* (leaf-derived callus)	MS media fortified with 2 µM BAP, 0.5 µM NAA, 10 µM PG promotes shoot organogenesis. Multiple shoots also can be regenerated from encapsulated nodes grown on MS medium supplemented with 3° µM BAP and 0.5 µM kinetin	Remya et al. (2013)
	A. tagala (nodal segment as explants)	Explants (79%) cultured showed shooting after culturing in MS 2 mg/m BAP and 0.5 mg/L NAA	Biswas et al. (2007)
	A. saccarta and *A. cathcartii* (nodal explant)	Application of BAP in combination with NAA showed better shoot induction in comparison to those hormones used separately	Sarma and Tanti (2017a)
	A. tagala (apical bud explant)	Addition of activated charcoal in culture media (MS media) help in circumventing the problem of polyphenol release of explant which hampered the regeneration of adventitious shoots	Remya et al. (2016)
	A. indica (nodal explants)	SH (Schenk and Hidebrandt) media fortified with 2.0 mg/L BAP and 0.5 mM spd (spermidine) showed best results with an average number of 47.5 base callus-derived shoots	Dey et al. (2020)
	A. indica (shoot tip, nodal segment, leaf disc callus, leaf segment)	Murashige and Skoog's medium with 0.54 µM α-naphthaleneacetic acid/NAA and 13.31 µM benzyladenine/BA promoted the regeneration of the maximum number of shoots (45–50) from nodal segment and shoot tip. The best results were observed in terms of shoot bud regeneration from leaf-derived callus while cultured on basal medium fortified with 2.69 µM NAA, 13.31 µM BA and 1.0 mg/l PG. Direct shoots organogenesis from leaf segments was done by using 13.31 µM BA along with 50 mg/L activated charcoal in MS basal medium	Manjula et al. (1997)

Table 2 (continued)

In vitro culture type	Plant	Result	Reference
In vitro root induction	*A. saccarta* (nodal explants)	IBA exhibited surpassing effect on number of rootlets and mean height of roots than NAA in *A. saccarta*	Sarma and Tanti (2017a)
	A. tagala (apical bud explant)	Regenerated shoots are rooted after culturing on MS medium with indole acetic acid/ IAA (1.5 µM), kinetin/KIN (1.5 µM) and 6-benzylaminopurine/BAP (0.5 µM)	Remya et al. (2016)
	A. indica (shoot tip, nodal segment, leaf disc callus, leaf segment)	Rooting the microshoots in White's medium supplemented with 2.46 µM IBA showed 85% survival rate	Manjula et al. (1997)
	A. indica (leaf-derived and nodal calli)	Rooting (80%) along with greater root length was observed in shoots regenerated from leaf-derived calli, while shoots from nodal calli displayed 95% rooting after culturing on MS media supplemented with 0.8 mg/L NAA	Pattar and Jayaraj (2012)
	A. indica (nodal explants)	Spermidine (0.5 µM) along with 1 mg/L IAA in MS media scaled up the rooting and lateral root development	Dey et al. (2020)
Somatic embryogenesis	*A. saccarta* and *A. cathcartii* (nodal explant)	Direct somatic embryogenesis was achieved after culturing the nodal explant on MS medium with different concentrations of BAP (1.0–4.0 mg/L) and 2iP (1.0–4.0 mg/L) separately or in combination with low concentration (0.5 and 1.0 mg/L) of auxin (NAA) respectively	Sarma and Tanti (2017a)
Synthetic seed production	*A. tagala* (nodal explants)	Artificial seeds were formed by encapsulating the nodes in 3% (m/v) sodium alginate and 1% (m/v) $CaCl_2$	Remya et al. (2013)
Acclimatization and hardening of plants	*A. bracteolata*	Survival rate (95%) of in vitro plants can be achieved when acclimatized to soil, farmyard, garden soil manure mixture in the ratio 1:1:1	Sebastinraj and Sidique, (2011)
	A. tagala	Survival rate (80%) rate of in vitro plants can be achieved when acclimatized to vermicute, soil mixture in the ratio 1:1	Remya et al. (2016)
	A. indica	Survival rate (95%) was observed when in vitro plantlets were acclimatized and hardened with White media and vermicute and transferred to greenhouse conditions	Manjula et al. (1997)
	A. tagala	Survival rate (80%) was noted when in vitro plantlets were hardened in plastic pots with soil and manure mixture in 1:1 ratio	Biswas et al. (2007)
	A. indica	Survival rate (100%) of in vitro plants were recorded after hardening the plantlets with autoclaved soil, sand, soilrite acclimatizing them by transferring to large pots with soil and soilrite ratio in ratio of 2:1	Dey et al. (2020)

Recently, to establish a protocol for micropropagation of *Artemisia annua* L, the optimum rooting was observed on the Murashige and Skoog (MS) medium supplemented with 0.1 mg/L IBA in leaf-derived calluses (Zayova et al. 2020).

According to Sebastinraj and Siddique (2011), Sarma and Tanti (2017a, b) and Biswas et al. (2007), IBA (indole-3-butyric acid) is most appropriate for in vitro rooting of *Aristolochia* in contrast to NAA and IAA (indoleacetic acid). On one hand, Sarma and Tanti (2017a, b) reported 0.5 mg/L IBA exhibited surpassing effect on a number of rootlets and mean height of roots than NAA in *A. saccarta*. Remya et al. (2016), on the other hand, observed efficient in vitro

rooting from apical bud explants of *A. tagala* on exposure to an amalgamation of IAA, BAP and KIN. Manjula et al. (1997) stated MS media and low ionic strength White media supplemented with precise concentration of IBA is effectual enough to initiate rhizogenesis and lateral root formation. In vitro rooting potency is also dependent upon the type of explant used. It was recorded by Pattar and Jayaraj (2012) that 80% rooting and greater root length were available in shoots from leaf-derived calli, but shoots from nodal calli displayed 95% rooting. In both cases, rooting was evident when MS media were supplemented with 0.8 mg/L NAA. The effect of other secondary metabolites on the in vitro rooting was put forward by Dey et al. (2020). They proved the fact how polyamine like spermidine (0.5 mM) along with IAA (1 mg/L) in MS media scaled up the rooting and lateral root development.

Somatic embryogenesis

This technology for in vitro propagation of endangered plants has been of immense focus on account of low propagation rate by seeds. The potential of somatic embryogenesis to regenerate plantlets is considered to be far more efficient than adventitious shoot, leaves and apical bud organogenesis. The in vitro propagation of elite palms through somatic embryogenesis is found to be advantageous for the high degree of variability, which will exist among improved progenies. By using such technologies, oil production from oil palm can be increased up to many degrees (Soh et al. 2011). For this context, somatic embryos of *Elaeis guineensis* Jacq (oil palm) were obtained after culturing the thin cell layer sections from the base of the explants in Murashige and Skoog (MS) medium supplemented with 450 µM picloram and 2,4-dichlorophenoxyacetic acid (2,4-D) with 3.0% sucrose, 500 mg /L glutamine, and 0.3 g/L activated charcoal and gelled with 2.5 g/L Phytagel for 12 weeks (Scherwinski-Pereira et al. 2010.

Very few reports have till now suggested methods to develop somatic embryo directly or in directly. Successful somatic embryo formation can be carried out by nodal explants cultured in different concentrations of 2-isopentenyl-adenine (2-iP) and benzylaminopurine (BAP) in combination with naphthaleneacetic acid (NAA) which permitted callus induction. *A. saccata* and *A. cathcartii* low concentrations of NAA positively influenced somatic embryo development, and there has been 88.3–96.6% success rate of regeneration of shoot from explants (Sarma and Tanti 2017b). *A. indicus*-directed callus induction up to 90% in 1:2 of NAA and BAP, respectively (Siddique et al. 2006). It was also observed in some cases cytokinin (Kinetin, BAP) and auxin (NAA, IAA) can be used in 1:2 ratio.

Synthetic seed production

Artificial seeds usually harbour the somatic embryo or explants from mother plant and are an excellent alternative to zygotic embryos as well as conventional plant breeding techniques. Plant species which have a drawback in terms of seed viability, inconvenience faced in vegetative propagation and storage can successfully propagate via synthetic seeds (Rihan et al. 2017). They help in the formation of multiple clones of the target plant thus preserving their genetical identity. To develop an efficient protocol for the production of the synthetic seeds of *Rhinacanthus nasutus* for their faster multiplication and isolation of Rhinacanthin-C, Rhinacanthin-D and Rhinacanthin-N, young healthy cotyledon explants were grown on MS medium supplemented with 4 mg/L 2, 4-D and 0.5 mg/L IBA to develop an embryonic callus. Those calluses are further cultured for 45 days in half-strength MS medium supplemented with 4.0 mg/L indole-3-butyric acid (IBA) to produce several somatic embryos. Somatic embryos at the torpedo stage were suspended in a matrix of MS medium supplemented with sodium alginate (3% W/V), and then dropped into the 100 mM calcium chloride ($CaCl_2{\cdot}2H_2O$) solution to generate the synthetic seeds. The optimum growth ability of the synthetic seed was evaluated on MS medium with 0.2 mg/L gibberellic acid (GA3) (Cheruvathur et al. 2013).

Remya et al. (2013) proposed a protocol for developing artificial seeds in commercially important plant *A. tagala*. In vitro shoot and nodal explants cultured in MS media were allowed to form the bead like seeds using different concentrations of sodium alginate and 1% $CaCl_2$. Most appropriate results were obtained at an intermediate concentration of sodium alginate, and maximum shoot formation was observed when these synthetic seeds were made to propagate in MS media supplemented with 3 µM BAP and 0.5 µM KIN.

Acclimatization and hardening of plants

Acclimatization and hardening are indispensable in order to ensure high chances of survival of in vitro plantlets. Direct transfer of the in vitro plants to the field can be detrimental. In order to overcome this drawback, certain approaches have been made. Sarma and Tanti (2017a, b) reported in vitro grown plantlets could be hardened by 1% w/v bavistine and irrigation with 0.5 × MS inorganic salts consecutively for 7 days. Acclimatization of plantlets was attained by exposing plantlets to aseptic culture room under controlled photoperiod and temperature for 2 weeks. Furthermore, the plantlets were exposed gradually to sunlight for acclimatization and were maintained in a garden. In *A. bracteolata*, 95% survival rate of in vitro plants were confirmed when acclimatized to soil, farmyard and garden soil manure in the ratio of 1:1:1 (Sebastinraj and Sidique 2011). Survival rate of 80% has been reported in *A. tagala* by Remya et al. (2016) when plantlets were acclimatized with vermicute and soil mixture (1:1). *A. indica* was seen to exhibit approx. 95% survival rate

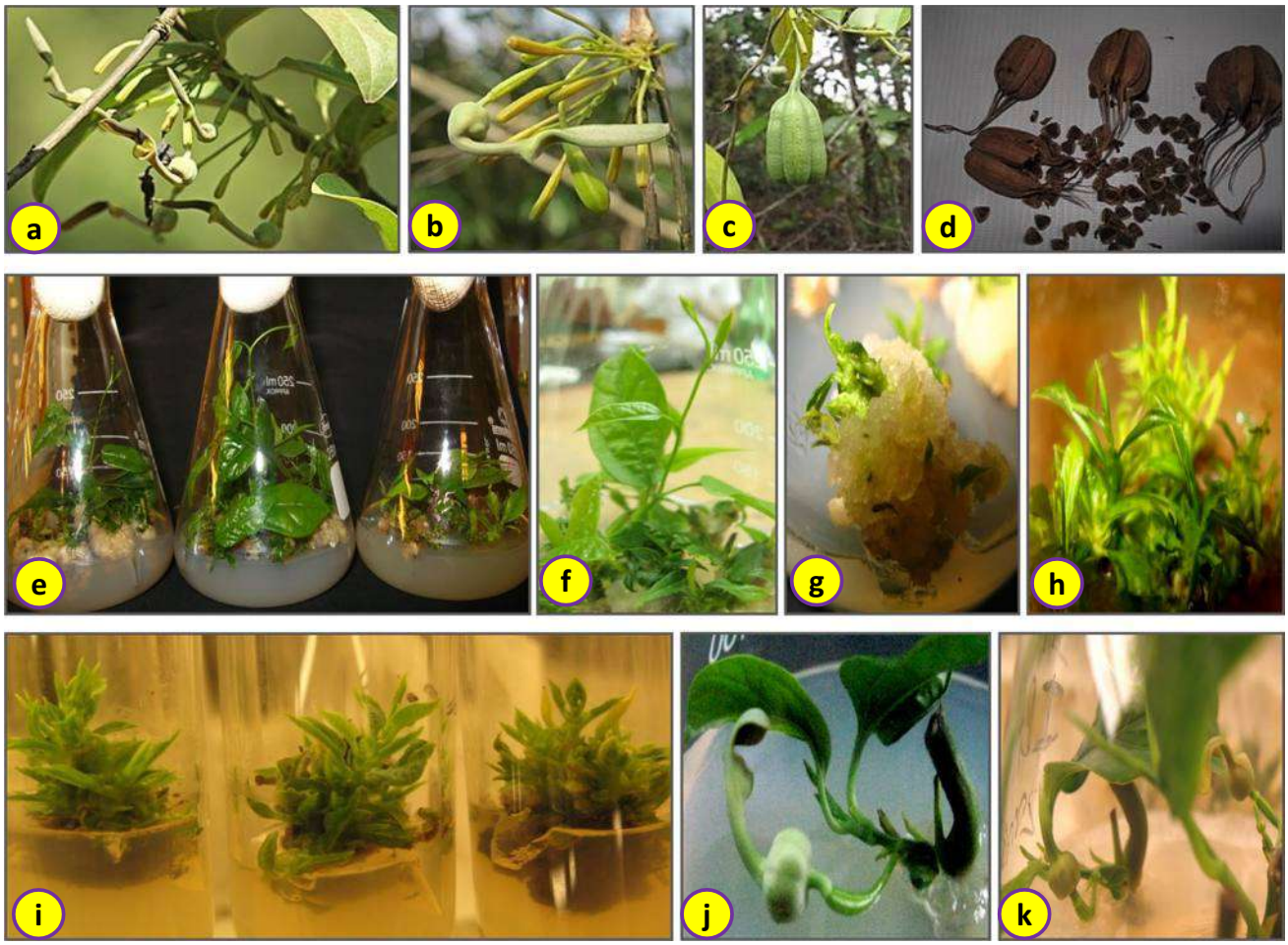

Fig. 3 *A. indica* **a** Habit, **b** Flowers, **c** Fruits, **d** Seeds (source: Wikimedia commons; Creative Commons Attribution-Share Alike 4.0 International); **e**, **f**, **g**, **h**, **i**. In vitro shoot multiplication and in vitro indirect regeneration from callus; **j**, **k** In vitro flowering (**e**–**k**: Abhijit Dey's own research photos)

when in vitro plantlets were hardened with White media and vermicute and transferred to greenhouse conditions (Manjula et al. 1997). Biswas et al (2007) also confirmed 80% survival rate when in vitro plantlets were hardened and acclimatized in plastic pots with 1:1 soil and manure. Survival rate of 100% of in vitro plants were noted when they were hardened with autoclaved soil, sand, soilrite and acclimatized by transferring to large pots, where soil and soilrite were in the ratio of 2:1 (Dey et al. 2020). Figure 3 presents various in vitro tools and biotechnological aspects for plant propagation, regeneration and flowering.

Biosynthesis and regulation of secondary metabolites

Aristolochia sp. is considered to be an essential plant owing to the wide range of pharmaceutically active secondary metabolites available in different parts of the plant. Terpenoids, steroids and phenolic compounds like lignans, coumarins; alkaloids like berberine, aristolochic acid, aristolactams, isoquinolines and benzylisoquinoline are major categories of components extracted from roots, leaves and stem (Kuo et al. 2012). β-Sitosterol and stigmasterol were two major steroids extracted from different plant parts of *Aristolochia* sp. Terpenoids are beneficial for its anti-inflammatory, antibacterial, antiviral and antirheumatic effects and have neutralizing potency against haemorrhagic effect (Dey and De 2011). Aristolochic acid has antisnake venom properties, but recently some reports have highlighted carcinogenic and nephrotoxic effects (Dey et al. 2020).

Biosynthesis of terpenoids

Comprehensive study of the terpenoid content of *Aristolochia* sp. has demonstrated the prevalence of sesquiterpenoids, monoterpenoids and deterpenoids from the plant extracts. Among these, sesquiterpene hydrocarbons like ishwarane, ishwarone, aristolochene, ishwarol, aristolactone, cadinanes,

aristolanes, beta caryophyllene, germacranes and bicyclogermacranes are present in considerable amounts. Pacheco et al. (2009) verified the presence of diterpenoid and its derivative compounds from *Aristolochia* sp. by isolating abundant kaurene, cledorane, labdane and assigned structures by ^{13}C-NMR. Aristolin, another terpenoid isolated, was found to be an ester of aristolochic acid and a diterpenoident-kauran-16-β, 17-diol (Kuo et al. 2012). Preistap et al. (2002) confirmed sesquiterpenes were more abundant, as compared to monoterpenes in leaves and stems. Ishwarone, the tricyclic precursor molecule of ishwarane, undergoes retrosynthetic removal of C8 resulting in the formation of octalone. Methylation of octalone resulted in the formation of decalone which in turn synthesized ishwarane via tertiary alcohols and octalin.

Biosynthesis of alkaloids

Since aristolochic acids are usually derived from benzylisoquinolinealakoids (BIA), having clear knowledge of their biosynthetic pathway is of utmost importance, as this data would be indispensable for having clarity regarding biosynthetic pathway of aristolochic acids. Cui et al. (2022) elucidated the BIA synthesis pathway using *Aristolochia contorta* as experimental model by genome-wide analysis and transcriptomic analysis. Tyrosine derivatives act as a precursor molecule in the pathway along with dopamine and 4 hydroxyphenylacetaldehyde which undergoes condensation in the presence of enzymes coded by NCS 70, 71 to form(S)-norcoclaurine. This product is catalysed by enzymatic activity of 6 OMT, CNMT, NMCH 4′OMT 67, 72–76 to yield s-reticuline as intermediate product. S-reticulline ultimately is responsible for synthesis of alkaloids like berberine.

Sustainable production of secondary metabolites by in vitro techniques

Owing to high demand of pharmaceutically active secondary metabolites in the drug industry, sustainable in vitro production of plants is becoming a necessity. One such instance is enhancing naturally low-calorie sweeteners (Steviol glycosides) obtained from *Stevia rebaudiana*. After culturing the 3-week-old in vitro plantlets on liquid woody plant medium (WPM) supplemented with 100 µM methyl jasmonate (MeJA) for 2 weeks, a 17-fold increase in stevioside production has been observed in comparison to the control plant (plantlet is grown without any elicitors) (Bayraktar et al. 2018). Also, hairy roots of *Nicotiana tabacum* L. cv. Petit Havana SR1 do not produce geraniol naturally. But after the genetic manipulation to express a plastid-targeted geraniol synthase gene isolated from *Valeriana officinalis* L. (VoGES) mediated by *Agrobacterium rhizogenes*, it was observed that the hairy roots can produce geraniol ranging from 13.7 to 31.3 µg/g dry weight (Ritala et al. 2014).

Massive exploitation of this perennial herb has eventually led to its classification as a critically endangered species. This approach is an effective conservational technique which is the sole solution to the exuberant harvesting of *Aristolochia* sp. from Western Ghats and Assam where it is endemic to. As of now, there are limited reports with respect to in vitro production on account of less comprehensible findings regarding the metabolic pathways involved. Certain works have also supported the fact that growth culture conditions and presence or absence of phytohormones precisely regulated the synthesis of secondary metabolites from explants.

Remya et al. (2016) reported the extraction of ishwarane, a tetracyclic sesquiterpene from in vitro plant leaves developed from apical bud explants. This particular method of in vitro regeneration of plantlets also confirmed the isolation of phenols, flavonoids, terpenoids and fatty acids in a sustainable quantity. Leaf-derived callus failed to report the absence of ishwarane but confirmed the presence of certain bioactive compounds unique to this in vitro approach. Alkaloid berberine was successfully isolated by Remya et al. (2016) by *both* in vitro techniques.

It is evident from many reports how culture media enriched with plant growth regulators, secondary metabolites can implement in vitro shooting, rooting, callus induction and multiplication. They are capable enough to simultaneously upgrade the synthesis of bioactive metabolites in in vitro plants. Dey et al. (2020) validated in vitro regeneration of *A. indica* to isolate aristolochic acid and analysed its endogenous level in in vitro shoots and roots. In this species of *Aristolochia* sp., nodal explant and apical shoot buds were cultured in SH media and were enriched with varying concentrations of polyamines (0.5 mM–1 mM) like putrescine, spermidine, spermine along with plant growth regulators auxin (IAA — 1.5 mg/L, IBA —1 mg/L) and cytokinin (KIN — 2 mg/L, BAP — 1.5 mg/L) to induce calli, direct shoot organogenesis and multiplied axillary shoot formation. Their HPLC study of the metabolite from in vitro regenerated plant extracts as well as mother plant illuminated the fact that aristolochic acid was higher in in vitro roots than plants grown under natural field conditions thus corroborating the pivotal role of polyamines in augmenting the concentration of aristolochic acid in combination with phytohormones.

Conclusions and future prospective

To combat the increasing demands of *Aristolochia* phytochemicals, sustainable conservational strategies are needed to be implemented. Several biotechnological interventions are already being performed to preserve the germplasms and produce economically important phytochemicals of

these genera. Studies elucidating the use of different markers (morphological, biochemical, molecular) to identify and assess variability among several species of *Aristolochia* are of prime use. This review is a small effort to gather the existing information and state the knowledge gaps for future works.

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Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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Cytokinin and abiotic stress tolerance -What has been accomplished and the way forward?

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More than a half-century has passed since it was discovered that phytohormone cytokinin (CK) is essential to drive cytokinesis and proliferation in plant tissue culture. Thereafter, cytokinin has emerged as the primary regulator of the plant cell cycle and numerous developmental processes. Lately, a growing body of evidence suggests that cytokinin has a role in mitigating both abiotic and biotic stress. Cytokinin is essential to defend plants against excessive light exposure and a unique kind of abiotic stress generated by an altered photoperiod. Secondly, cytokinin also exhibits multi-stress resilience under changing environments. Furthermore, cytokinin homeostasis is also affected by several forms of stress. Therefore, the diverse roles of cytokinin in reaction to stress, as well as its interactions with other hormones, are discussed in detail. When it comes to agriculture, understanding the functioning processes of cytokinins under changing environmental conditions can assist in utilizing the

phytohormone, to increase productivity. Through this review, we briefly describe the biological role of cytokinin in enhancing the performance of plants growth under abiotic challenges as well as the probable mechanisms underpinning cytokinin-induced stress tolerance. In addition, the article lays forth a strategy for using biotechnological tools to modify genes in the cytokinin pathway to engineer abiotic stress tolerance in plants. The information presented here will assist in better understanding the function of cytokinin in plants and their effective investigation in the cropping system.

KEYWORDS

cytokinin (CK), CK metabolic genes, CK signaling genes, abiotic stress, crop resilience, genome editing

Challenging environmental factors and cytokinin

Climate change and rapid population growth pose enormous hurdles to achieving food security, which remains a primary concern for all stakeholders and governments (Muluneh, 2021; Dasgupta and Robinson, 2022). Feeding the rapidly expanding global population, which is anticipated to exceed 10 billion people by 2050 and needs 49% additional food, is a major challenge (Ahmar et al., 2020). There are already 820 million people in the world who are chronically undernourished, and this figure is expected to rise sharply in the future years, further compromising global food security (FAOSTAT, 2020). In addition, the hidden hunger is considerably worse today than it was a decade ago in Africa, Western Asia, and other developing nations (FAO et al., 2018). Furthermore, food production is being hampered by unusual weather circumstances connected to environmental degradation and rising land competition as a result of urbanization (Lobell and Gourdji, 2012; Lenaerts et al., 2019). Climate change is expected to raise the earth's temperature, resulting in global warming, irregular rain patterns, and the intensification of various abiotic and biotic pressures, all of which significantly reduce agricultural yields (Raza et al., 2019). In the future, changing climate is expected to become more prevalent and aggravate different stress, posing major concerns to agricultural yield (Ray et al., 2013). In order to ensure sustainable agricultural production in the face of changing climatic and growing population, yearly crop yields must be increased (Tilman et al., 2011; Ray et al., 2013). Therefore, to address these multi-dimensional challenges, agricultural production systems must undergo a significant transition (Lenaerts et al., 2019). Sustainable agricultural production may be aided by the use of sustainable resources to boost crop yield per unit area and the effective usage of fertilizer and water. In order to alleviate the hidden and chronic hunger, economic development is essential, but it may not be sufficient to eradicate hunger (Lenaerts and Demont 2021). For thousands of years, plant breeding has been one of the most important strategies to fulfil people's food needs *via* crop domestication (Ahmar et al., 2020).

Cytokinins are family of adenine-derived phytohormones characterised by the presence of an aromatic chain or isoprenoid at the N6 position of their adenine moiety (Mok and Mok, 2001). Cytokinins are typically defined as growth-promoting hormones, despite the fact that diverse substance with cytokinin action have been found to regulate wide range of developmental and physiological processes in plants. In the 1950s, Miller and Skoog identified the first cytokinin, kinetin, which was classified as a plant-derived molecule that accelerated cell division (Miller et al., 1956). A further investigation found that kinetin, in conjunction with auxin, was important for stimulating organ development and cell division in undifferentiated cells culture (Skoog and Miller, 1957). Despite the fact that the cytokinin study began in the mid-1900s, it is an ancient hormone, having emerged as one of the earliest hormones in photosynthetically competent organisms (Wang et al., 2015). According to evolutionary research, the genetic sequences that are orthologs to known components of the cytokinin signaling pathway may be found in the common ancestor of all land plants, charophytes (Wang et al., 2015). These findings indicate that cytokinin had a function in plants as far back as 450 million years. In addition, cytokinins are recognized for their role in plant growth, development, senescence delay, and modulation of biotic and abiotic stress tolerance (Kieber and Schaller, 2018; Cortleven et al., 2019).

Changes in chemoattractant, temperature, nutrient content, and osmotic conditions all activate cytokinin signaling cascades, which are evolutionarily connected to the two-component systems in unicellular organisms that engage in signal transduction (Hwang et al., 2002; Wolanin et al., 2002). Cytokinins perform critical and multifaceted functions in plant development and abiotic stress responses (Ha et al., 2012; Hwang et al., 2012; Zwack and Rashotte, 2015). Several research have shown that cytokinins have both positive and negative impacts on stress tolerance or resistance (Ghanem et al., 2008; Nishiyama et al., 2011). Plants, on the other hand, may experience both a short-term and long-term rise in cytokinin levels when they are exposed to extreme stress conditions (Alvarez et al., 2008; Dobra et al., 2010). For instance, cytokinin synthesis *IPT* genes (adenosine phosphate isopentenyl transferases) are up-regulated upon salt (NaCl) treatment, and a mutation in cytokinin biosynthesis leads to a robust salt-tolerant phenotype (Nishiyama et al., 2011). The impact of exogenous cytokinin administration on abiotic stress tolerance have been the subject of several investigations. *Triticum*

aestivum (wheat) seedlings that receive exogenous cytokinins application are more tolerant to salt stress, whereas a similar treatment on *Phaseolus vulgaris* (beans) result in more susceptible phenotype to the salt stress (Kirkham et al., 1974; Abdullah and Ahmad, 1990). Furthermore, Arabidopsis plants displayed enhanced ability to survivie freezing or dehydration after being treated with endogenous cytokinin (Jones et al., 2010; Kang et al., 2012).

Transgenic plants that overexpress cytokinin biosynthesis genes (*IPTs*) or cytokinin degradation genes (*CKXs*) demonstrate the impact of altered endogenous cytokinin levels. More importantly, the overproduction of endogenous cytokinin enhances drought stress tolerance in many plants. However, reduced cytokinin levels, on the other hand, have a positive impact on drought tolerance (Werner et al., 2010; Qin et al., 2011; Macková et al., 2013; Li et al., 2021). Additionally, the cytokinin signaling components play a significant role in abiotic stress tolerance. For example, Arabidopsis *AHK1*, a histidine kinase 1 involved in cytokinin signaling, acts as a positive regulator of salt and drought stress responses. Furthermore, the loss-of-function mutant phenotype in *ahk2*, *ahk3*, and *ahk2 ahk3* in Arabidopsis is associated with increased tolerance to salt and drought stress (Wohlbach et al., 2008; Kumar et al., 2013). Drought stress responses are negatively and redundantly regulated by AHPs (histidine phosphotransfer proteins) (Hwang et al., 2012; Nishiyama et al., 2013). However, in salt stress resistance phenotype in Arabidopsis was discovered while researching the quadruple loss-of-function mutant *arr3arr4arr5arr6* (Mason et al., 2010). These early finding indicated that cytokinin metabolism and signaling genes play an important role in responding to diverse environmental stress conditions.

Cytokinin, on the other hand, cannot reduce abiotic stress on its own; instead, it functions in conjunction with other signaling pathways (Antoniadi et al., 2020; Li et al., 2021). There is a wealth of information available on the function of cytokinin and its interactions with other phytohormones when plants are exposed to abiotic stress. So, this review exemplifies the regulatory role of cytokinin in abiotic stress tolerance and activation of possible novel crosstalk with other key stress phytohormones. In this review, we provide an inclusive overview of the advancement of genetic approaches in dissecting the function of cytokinin signaling components in regulating stress tolerance in plants under challenging environments stress, followed by brief insights into future approaches.

Plant mechanisms for sensing and response to abiotic stress

At the cellular level, several abiotic stressors such as drought, heat, cold, and salt may produce common cell disruptions and secondary stress such as membrane damage, reactive oxygen species (ROS) production and damage, protein denaturation, and osmotic stress (Figure 1). In general, the initial step in the stress response is perception, which is followed by the transmission of information through secondary messengers to regulators and, eventually, to effectors, which are responsible for the protective function. A sensor is a biological molecule that may detect an unfavourable change in its surrounding environment and immediately elicit a reaction by triggering the production of signal molecules inside the plant system. In general, receptors or membrane-associated proteins pick up on stresses, which causes an ionic imbalance across the membrane. Stresses caused by drought, heat, cold, and salt all induce an increase in the quantity of Ca^{2+} (signal molecules) that enters the cytoplasm of the cell from either its own reserves or an apoplastic source. One form of sensor for the stress signals is thought to be the passages that govern Ca^{2+} entrance (Aftab et al., 2021; Javaid et al., 2022; Paes de Melo et al., 2022). Other than Ca^{2+}, ROS and nitric oxide (NO) are other messenger molecules involved in inducing plant response to cold stress. Plants generate ROS such as superoxide (O_2), hydroxyl radicals (OH), and hydrogen peroxide (H_2O_2) in order to defend themselves against the diverse stress that they are exposed (He et al., 2018). In receptor-like kinases (RLKs), there is an extracellular domain, a transmembrane domain, and an intracellular kinase domain. The extracellular domain is where ligands bind, and the transmembrane domain is where protein-protein interactions take place (Ku et al., 2018). The histidine residue in the intracellular kinase domain is auto-phosphorylated when the ligand or signal binds to the extracellular domain, and the phosphoryl moiety is received by the aspartate receiver section of the sensor protein or a different protein (Yadav et al., 2021). After then, the activated sensor protein (or proteins) may either directly phosphorylate particular targets or trigger cellular responses that are unique to the signal that was received via the mitogen-activated protein kinase (MAPK) cascade. Protein phosphorylation and dephosphorylation, which are both forms of the intracellular signaling mode, govern a broad variety of cellular functions, including the activation of enzymes, assembly of macromolecules, localization of proteins, and their breakdown (Yadav et al., 2021). Plants are able to detect when they are being subjected to abiotic stress, which triggers a series of signaling cascades that activate ion channels, kinase cascades, the formation of ROS, and the accumulation of plant hormones, which ultimately leads to the induction of the expression of specific subsets of genes that are responsible combating the abiotic stress (Ku et al., 2018; Zandalinas et al., 2020). If the plant's stress-coping systems are ineffective in reducing the negative consequences of stress, mostly due to ROS accumulation, the cells activate environmental-triggered cell death processes, which include the plant's senescence (Zandalinas et al., 2020).

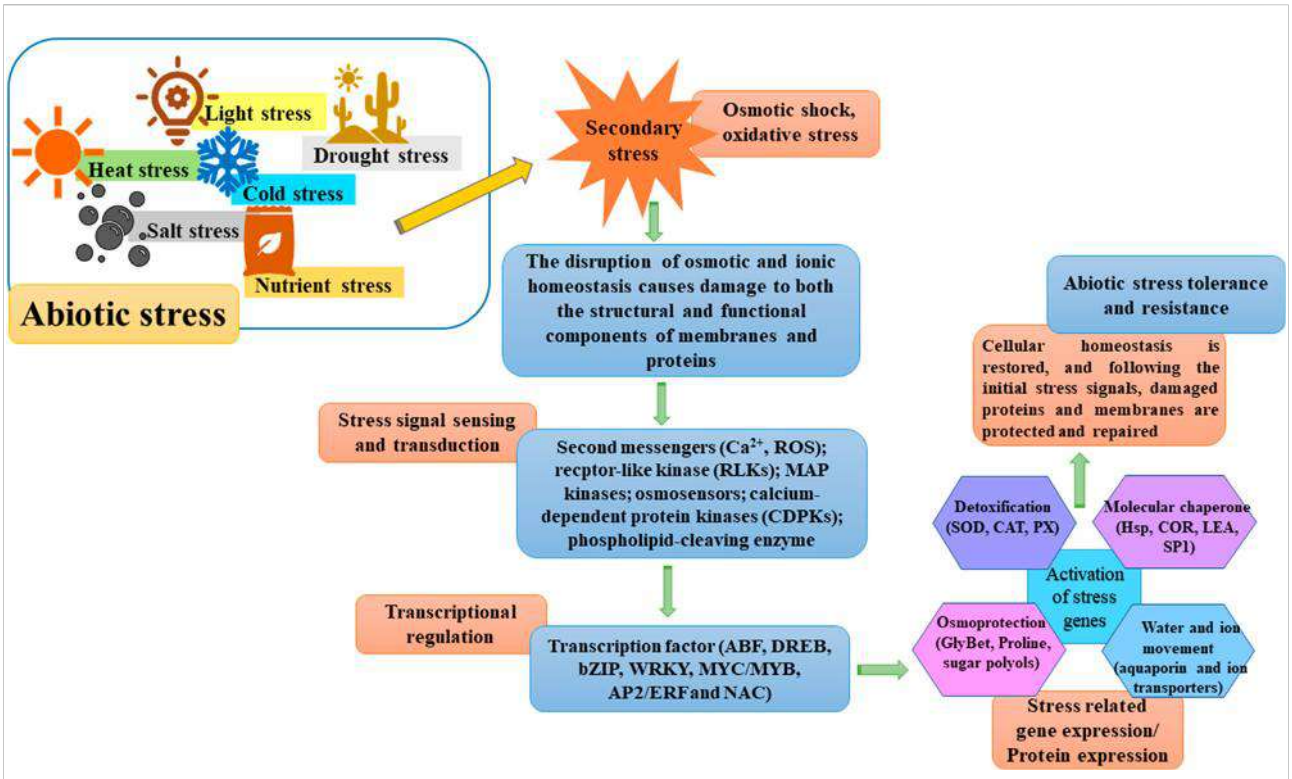

FIGURE 1
A simplified schematic representation of mechanism through which plant responses to diverse abiotic stress. The general signaling pathways in plants that are activated in response to abiotic stress, beginning with signal perception and leading to the stress responses. Cold, drought, light, nutrient and salinity frequently induce cellular damage and secondary osmotic and oxidative stress. Following upstream signaling processes and transcriptional controls activate stress-responsive mechanisms in order to restore cellular homeostasis and protect and repair damaged proteins and membranes after the initial stress signals (e.g., changes in temperature or osmotic and ionic effects or membrane fluidity). ABF, ABA responsive element (ABRE) binding factor; AP2/ERF, Apetala2/Ethylene Responsive Factor; bZIP, basic leucine zipper transcription factor; CAT, catalase; CBF/DREB, C-repeat-binding factor/dehydration-responsive-binding protein; CDPK, calcium-dependent protein kinase; COR, cold-responsive protein; HK1, histidine kinase-1; Hsp, heat-shock protein; ICE1, inducer of CBF expression 1; LEA, late embryogenesis abundant; MAP, mitogen-activated protein; PLD, phospholipase D; PX, peroxidase; ROS, reactive oxygen species; SOD, superoxide dismutase; and SP1, stable protein 1.

Cytokinin in plant development and stress adaptation

Cytokinins are a family of plant hormones that are fundamental to a variety of growth and development processes (Pavlů et al., 2018). Cytokinins have been widely investigated for their metabolism, signal transduction pathway, chemical composition, and their role in plant growth and development, since their discovery in *Zea mays* (maize) seeds over 50 years ago (Figure 2). Inhibition of lateral root initiation, regulation of cell division, differentiation of metaxylem and phloem in roots, photomorphogenic cell differentiation in shoots and expanding leaves and inhibition or delaying of leaf senescence are all-important regulatory activity of cytokinins at the tissue and organ levels (Bielach et al., 2012; Chiang et al., 2012; Efroni et al., 2013; Zwack et al., 2015).

Adenine derivatives with aromatic side chains or isoprenoid make up the endogenous cytokinin. Isoprenoid cytokinin, which is abundant in nature, may be classified as trans-zeatin (tZ)-, isopentenyladenine (iP)-, cis-zeatin (cZ)-, or dihydrozeatin (DHZ)-type derivatives based on the side chain hydroxylation or reduction. In comparison, aromatic cytokinins, such as N6-(meta-hydroxybenzyl) adenine (BA), are less abundant in plants (Faiss et al., 1997). The isoprenoid cytokinins vary from one another in terms of their biological roles, metabolic conversions, biochemical characteristics, and transportability throughout the plant system (Pavlů et al., 2018). Cytokinin homeostasis is maintained by a number of enzymes engaged in cytokinin metabolism, including those involved in cytokinin production, inter-conversion between cytokinin types, and cytokinin degradation (Thu et al., 2017; Skalak et al., 2021). The role of a wide variety of genes and enzymes, along with the composed metabolic network controlled by cytokinins across the plant kingdom, has been thoroughly investigated (Zwack et al., 2015; Pavlů et al., 2018). The phospho-relay cascades of the two-component system (TCS) are established and lead to the expression regulation of specific genes involved in plant adaptation when the cytokinin signaling pathway is triggered by

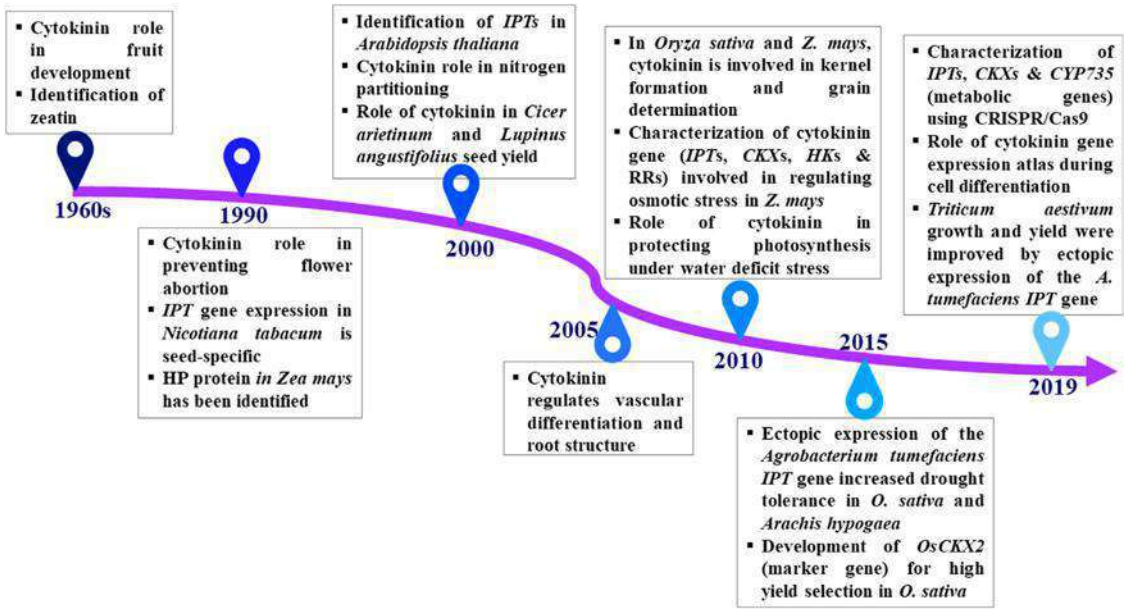

FIGURE 2
Cytokinin timeline: from discovery to crop plant application. A chronology of significant advancements in cytokinin research. Abbreviation: CKXs, CK oxidases/dehydrogenases; RRs, cytokinin response regulators; IPTs, isopentenyl transferases; HK, histidine kinas.

various environmental stimuli, like nutrition levels, changes in temperature, and osmotic conditions (Thu et al., 2017; Pavlů et al., 2018). Most recently, it was shown that cytokinin interacts with jasmonates (JAs), ethylene (ET), salicylic acid (SA), and abscisic acid (ABA), showing the presence of an interconnected coordinating network among the phytohormones involved in plant stress tolerance (Efroni et al., 2013; Thu et al., 2017; Artner and Benkova, 2019; Antoniadi et al., 2020; Skalak et al., 2021). Additionally, it is well established that cytokinin biosynthesis and signalling components operate as constitutive signals defining the plant response to drought stress and controlling drought acclimatization. Because of their spatiotemporal expression, rapid responses, and widely associated pathways, cytokinins are an ideal candidate for regulating complicated morphogenetic processes under water stress. We will highlight the importance of plant cytokinins and their regulation under abiotic stress in this review and will offer an approach to understanding the function and regulation of cytokinins in plants.

Role of cytokinin in plant response and regulation to abiotic stress

Multiple aspects of plant growth and development are regulated by the phytohormone cytokinin. A significant number of mutants have been created in the cytokinin signaling pathway, biosynthesis, and breakdown processes, which has resulted in the rapid advancement in the field of cytokinin (Li et al., 2021; Prasad, 2022). According to research, cytokinins are important signaling molecules that trigger a range of plant stress responses. Moreover, abiotic stress has a direct effect on cytokinin transport, responses, and concentrations. Table 1 summarizes the genes from cytokinin pathways investigated so far that react to various abiotic stresses, in addition to their involvement in stress tolerance. We focused on nutrient, light, heat, drought, cold, and salt stress in this review to highlight the function of cytokinin in abiotic stress response and it is potential to increase abiotic stress tolerance (Figure 3).

Nutrient deficiency stress

Stress caused by nutrient deficiency in the soil triggers a number of reactions, all of which include cytokinin at varying levels (Pavlů et al., 2018). Root system architecture (RSA) is modified by the nutrients availability, and cytokinin is one of the important components that regulate RSA in response to availability of nutritional signals (Kroevoets et al., 2016). Nutritional signals affect the transcript levels of cytokinin metabolism and signaling genes, which are both implicated in regulating RSA (Bielach et al., 2012; Ramireddy et al., 2014; Chang et al., 2015; Pavlů et al., 2018). Cytokinin modulates the

TABLE 1 A summary of genetic research aimed at elucidating the function of cytokinin in the response to abiotic stress.

S. No	Plant species	Target genes	Expression under stress conditions	Genetic approach	Significant outcome	Reference
Cytokinin biosynthesis						
1	*Solanum lycopersicum*	*SlIPT3*	Strongly repressed in roots under salt stress	*35S:SlIPT3*	Improved tolerance to salinity	Žižková et al. (2015)
2	*Arabidopsis thaliana*	*IPT3*		*ipt3*		Žižková et al. (2015)
3	*S. lycopersicum*	*SlIPT4*	Strongly repressed in roots under salt stress			Žižková et al. (2015)
4	*A. thaliana*	*IPT8*		*ER:IPT8*, estradiol-inducible	Reduce plant tolerance under salt and osmotic stress	Wang et al. (2015)
5	*A. thaliana*	*IPT1*; *IPT3 IPT5*; *IPT7*		*ipt1 ipt3 ipt5 ipt7*	Increased resistance to salt stress, drought stress	Nishiyama et al. (2011)
6	*A. thaliana*	*CKX1*		*bGLU:CKX1 in barley*	Increased resistance to drought stress	Pospíšilová et al. (2016)
7	*O. sativa*	*OsCKX2*		*OsCKX2-RNAi*	Increased resistance to salinity stress	Joshi et al. (2017)
8	*O. sativa*	*OsLOG*	Downregulated by cold, drought and salt stress			Tripathi et al. (2012)
Cytokinin homeostasis						
9	*A. thaliana*	*UGT76C2*	Downregulated by osmotic stress and drought stresses	*35S:UGT76C2*	Tolerant to drought stress as adult plants	Li et al. (2015)
10	*A. thaliana*	*UGT76C2*		*ugt76c2*	More sensitive to drought stress	Li et al. (2015)
Cytokinin signaling						
11	*A. thaliana*	*AHK1*	Induced by dehydration	AHK1 overexpressor	Tolerant to drought stress	Liu et al. (2008)
12	*A. thaliana*	*AHK2*	Downregulated by salt			Buer et al. (2004)
13	*A. thaliana*	*AHK2*	Induced by dehydration	*ahk2*	Increased survival to drought after rewatering, increased survival upon salt stress	Liu et al., 2008; Argyros et al., 2008
14	*A. thaliana*	*AHK2*		*ahk2-2*	Hypersensitive to salt stress in terms of root growth and fresh weight	Zürcher et al. (2016)
15	*A. thaliana*	*AHK3*	Induced by hydration, high salinity and cold stress (3-week-old plants)	*ahk3*	Drought and salinity tolerant	Liu et al. (2008)
16	*A. thaliana*	*AHK3*	Not responsive to cold (11-day-old seedlings)	*ahk3*	Enhanced drought tolerance	Argyros et al., 2008; Tran et al., 2007
17	*A. thaliana*	*AHK3*		*ahk3-3*	Increased root elongation after transfer to low water potential media	Zürcher et al. (2016)
18	*A. thaliana*	*AHK2 AHK3*		*ahk2 ahk3*	More tolerant to drought and salt than single	Liu et al. (2008)
19	*A. thaliana*	*AHK2 AHK3*		*ahk2 ahk3*	Enhanced cold tolerance	Argyros et al. (2008)
		AHK3 AHK4		*ahk3 ahk4*		
20	*A. thaliana*	*AHK4*	Induced by dehydration			Liu et al. (2008)
21	*O. sativa*	*OsAHP1*		OsAHP-RNAi	Hypersensitive to salt treatment but resistant to osmotic stress	Jeon et al. (2013)
22	*A. thaliana*	*AHP2*	Downregulated by dehydration	*ahp2 ahp3 ahp5*	Strong drought-tolerant phenotype	Jeon et al. (2010)
23	*O. sativa*	*OsAHP2*		OsAHP-RNAi	Hypersensitive to salt treatment but resistant to osmotic stress	Jeon et al. (2013)
24	*A. thaliana*	*AHP3*	Downregulated by dehydration	*ahp2 ahp3 ahp5*	Strong drought-tolerant phenotype	Jeon et al. (2010)

(Continued on following page)

TABLE 1 (*Continued*) A summary of genetic research aimed at elucidating the function of cytokinin in the response to abiotic stress.

S. No	Plant species	Target genes	Expression under stress conditions	Genetic approach	Significant outcome	Reference
25	*A. thaliana*	*AHP5*	Downregulated by dehydration	*ahp2 ahp3 ahp5*	Strong drought-tolerant phenotype	Jeon et al. (2013)
	A. thaliana			*ahp2 ahp3 ahp5*	Reduced type A *ARR* expression in response to cold	Sakai et al. (1998)
26	*A. thaliana*	*ARR1*		*35S:ARR1*	Hypersensitive cold response of type A *ARR*s as well as enhanced cold tolerance	Sakai et al. (1998)
27	*A. thaliana*	*ARR5*	Induced by cold, salinity and dehydration			Ha et al., 2013; Sakai et al., 2000
		ARR6				
28	*A. thaliana*	*ARR7*	Induced by cold, salinity and dehydration	*35S:ARR7*	Hypersensitive response to cold temperatures	Ha et al., 2013, Argyros et al., 2008
29	*A. thaliana*	*ARR9*	Weak and early induction by cold, downregulated by heat			Skalák et al., 2016; Ha et al., 2013
		ARR10				
30	*A. thaliana*	*ARR12*	Downregulated by heat stress	*arr1 arr12*	Less sensitive to salt stress	Skalák et al., 2016; Kang et al., 2013
31	*A. thaliana*	*ARR15*	Induced by cold, salinity and dehydration			Ha et al., 2013; Sakai et al., 2000
32	*A. thaliana*	*ARR22*	Weak and late induction by cold, induced by drought			Ha et al., 2013; Sakai et al., 2000
Cytokinin response						
33	*S. lycopersicum*	*SlCRF1*	Induced by cold in leaves and roots, repressed by heat in roots			Brenner et al. (2012)
34	*S. lycopersicum*	*SlCRF1*	Slightly reduced in leaves and strongly decreased in roots by drought			Brenner et al. (2012)
35	*S. lycopersicum*	*SlCRF2*	Induced by H_2O_2 treatment only in roots			Brenner et al. (2012)
36	*A. thaliana*	*CRF4*	Strongly induced in both root and shoot tissues by cold	*35S:CRF4*	Tolerant to cold treatment	Kang et al. (2012)
37	*A. thaliana*	*CRF4*		*crf4*	Sensitive to cold treatment	Kang et al. (2012)
38	*A. thaliana*	*CRF6*	Induced by heat shock, oxidative (H_2O_2) and salt stress			Reguera et al., 2013

expression of various transporter genes as well as the development of passage cells, which affects the plant's capacity to absorb nutrients (Werner et al., 2010; Andersen et al., 2018). As a result, cytokinin governs physiological and morphological adaptive responses to nutritional stress to survive. Furthermore, a study of the phosphate deprivation response in *Arabidopsis thaliana* mutants found that cytokinin signaling is essential for a significant response to decrease phosphate availability. This was the first study to demonstrate a specialized function for cytokinin signalling in nutritional sensing. (Franco-Zorrilla et al., 2002; Franco-Zorrilla, Martín et al., 2005). Sulfate transporter genes are suppressed by cytokinin, which is a negative regulator of sulphur acquisition (Maruyama-Nakashita et al., 2004). Cytokinin also inhibits genes involved in iron absorption and iron homeostasis (Séguéla et al., 2008). Cytokinin controls sodium (Na) build up through the sodium transporter gene *HKT1;1* as previously stated (Mason et al., 2010). Low potassium levels or an artificially reduced cytokinin status resulted in upregulation of the high-affinity K^+ transporter gene *HAK5*, promotes root hair development, and accelerates ROS accumulation, indicating that cytokinin plays a role in responding to low potassium availability (Nam et al., 2012). However, another micronutrient, boron (B), was reported in *Brassica napus* seedlings to be linked to enhanced cytokinin content, which was thought to be a prerequisite for a different growth response (Eggert and von Wirén, 2017). Cytokinin is a key regulator in plant arsenic (As) stress adaptation (Mohan et al., 2016). Reduced cytokinin status was shown to make *A. thaliana* plants more resistant to arsenate, which is the most prevalent form of arsenic (As). Cytokinin deficit boosted the expression of As (V)/phosphate transporter genes and arsenate stress tolerance machinery, resulting in the aggregation of complexing agents (Mohan et al., 2016).

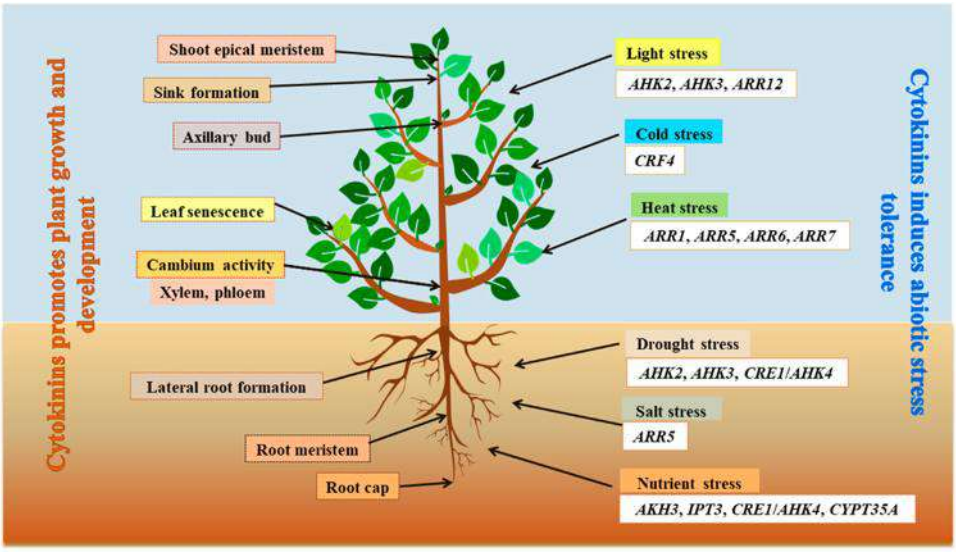

FIGURE 3
Cytokinins function in plant development and abiotic stress. Schematic illustration of cytokinin as a signaling molecule that regulates key plant developmental processes and its response to various abiotic stress.

Higher cytokinin levels, on the other hand, induced tolerance to another soil pollutant, selenium (Se) (Lehotai et al., 2012). Subsequently these findings imply that cytokinin has a role in the regulation of As and Se stress adaption. Cytokinins capacity to regulate plant development in response to nutrient stress was demonstrated in recent research on the role of cytokinin in signaling the availability of nitrogen (N) from the roots to the shoots (Landrein et al., 2018; Poitout et al., 2018). The expression of a GFP reporter gene under the control of WUS promoter, that governs the expression of a key regulator of shoot apical meristem (SAM) activity, was measured using quantitative microscopy (Landrein et al., 2018). The analysis of reporter gene activation in the context of cytokinin metabolism mutants indicated that IPTs were necessary for *de novo* synthesizes of cytokinin in response to changed N supply in the soil. Increases in soil N content consistently enhances the concentration of tZR, which is the primary cytokinin transport form. The reaction of the *pWUS::GFP* reporter gene to changing N availability happened quickly in the SAM, occurring within 24 h. Notably, grafting experiments between WT and cytokinin mutant plants demonstrated that while precursors to active cytokinins can be synthesized in the root (or elsewhere in the plant), the reporter gene response dependents solely on the ability of the shoot to form active cytokinins, presumably via LOG enzymes in the SAM (Chickarmane et al., 2012). Many studies have identified WUS as a primary target gene of RRBs (type-B response regulator proteins), suggesting a shorter signalling channel in the responsive meristem, which is consistent with cytokinin working *via* altering *WUS* activity (Dai et al., 2017). Poitout et al. (2018) determined that the ABCG14 transporter plays a critical role in the export of nitrate-induced cytokinin from roots, based on the fact that its mutation affected systemic N (nitrogen) signalling. Furthermore, they discovered a significant transcriptional reprogramming in shoots mediated by root-derived cytokinin, indicating that the hormone has functions beyond regulating SAM activity (Poitout et al., 2018). NLP transcription factors (TF), which act as positive regulators of *CYP735A* and *IPT* gene expression, are involved in the increase of cytokinin levels in the root in response to changes in nitrate availability. On the other hand, NIGT1 TF, which are also positively regulated by NLPs, act as negative regulators of *CYP735A* and *IPT* gene expression. (Maeda et al., 2018). The perennial grass *Lolium perenne* (Guo et al., 2017) produced results showing a role for cytokinin as a systemic N signal, implying that the function is evolutionarily conserved (Guo et al., 2017). Overall, it has been shown that cytokinin production in the root and translocation to the shoot contains significant information about soil conditions, particularly N availability, to the shoot, allowing the latter to control its own activity.

Light stress

In addition to supplying energy for photosynthesis, light transmits information about the time of day and season, and it has an impact on the direction in which plants are growing. Excessive or insufficient light stress plants and new research

TABLE 2 A list of CK signaling genes involved in the development of abiotic stress-tolerant plants.

S. No.	Gene	Response to stress	Host plant	Genetic engineering approach	References
1	*ARR1*	↑Heat tolerance	*Arabidopsis thaliana*	Constitutive overexpression	Karunadasa et al. (2022)
2	*TaIPT8*	↑Drought tolerance	Wheat (*Triticum aestivum*)	CRISPR/Cas9-based gene editing and constitutive overexpression	Wang et al. (2022)
3	*IPT*	↑Salt tolerance	*Nicotiana tabacum*	Stress-inducible senescence overexpression	Avni et al. (2020)
4	*OsERA1*	↑Drought tolerance	Rice (*Oryza sativa*)	CRISPR/Cas9	Ogata et al. (2020)
5	*IPT*	↑Drought tolerance	Creeping bentgrass (*Agrostis stolonifera*)	Stress-inducible overexpression	Xu et al. (2017)
6	*CKX1*	↑Drought tolerance	Barley (*Hordeum vulgare*)	Constitutive overexpression	Pospíšilová et al. (2016)
7	*CKX1*	↑Drought tolerance	*N. tabacum*	Constitutive overexpression	Lubovská et al. (2014)
8	*IPT*	↑Zinc tolerance, ↓leaf senescence	*N. tabacum*	Senescence-inducible overexpression	Pavlíková et al. (2014)
9	*AHP2, AHP3, AHP5*	↑Drought tolerance	*A. thaliana*	Knockout	Nishiyama et al. (2013)
10	*ARR22*	↑Drought, ↑cold tolerance	*A. thaliana*	Constitutive overexpression	Kang et al. (2013)
11	*IPT*	↑Drought tolerance, ↓leaf senescence	Cotton (*Gossypium hirsutum*)	Senescence-inducible overexpression	Kuppu et al. (2013)
12	*IPT*	↑Cold tolerance, ↓leaf senescence	*Saccharum* spp.	Stress-inducible overexpression	Belintani et al. (2012)
13	*IPT*	↑Salt tolerance, ↓leaf senescence	*N. tabacum*	Stress-inducible overexpression	Qiu et al. (2012)
14	*IPT*	↑Salt tolerance, ↓leaf senescence	Cotton (*G. hirsutum*)	Senescence-inducible overexpression	Liu et al. (2012)
15	*AHK2, AHK3*	↑Drought, ↑cold, ↑salt tolerance	*A. thaliana*	Knockout	Kang et al. (2012)
16	*CKX1, CKX2, CKX3, CKX4*	↑Drought, ↑salt tolerance	*A. thaliana*	Constitutive overexpression	Nishiyama et al. (2011)
17	*IPT1, 3, 5, 7*	↑Drought, ↑salt tolerance	*A. thaliana*	Knockout	Nishiyama et al. (2011)

↑: Increase, ↓: Decrease.

indicates that an altered day/night cycle may also stress plants (Bhaskar et al., 2021; Li et al., 2021). The response to these pressures involves cytokinin at several levels, which will be briefly summarized in the sections that follows. Even though photosynthesis needs light, too much light can harm the photosynthetic apparatus as well as other parts of the cell. To prevent being stressed by too much light (high light stress), plants have evolved a number of defensive mechanisms, including the cyclic electron transport, disposal of excess light energy as heat, and light avoidance motions of chloroplasts and leaves (Takahashi and Badger, 2011). However, even with these protective mechanisms, exposure to excessive levels of light may induce an over reduction of the photosynthetic electron transport chain, resulting in photoinhibition, which reduces the efficiency of photosynthesis (Yamamoto, 2016). In particular, protein D1, which is a component of the reaction centre of photosystem II (PSII), is one of the most often affected by UV radiation (Edelman and Mattoo, 2008). Reduced cytokinin status resulted in lower photoprotection and increased photoinhibition in plants, owing to a significant fall in the D1 level (Cortleven et al., 2014). Additionally, due to inadequate D1 repair, cytokinin-deficient plants had a reduced ability to recover from photoinhibition after high light stress. Plants antioxidant capacity was also lowered as a result of a lack of cytokinin. Thus, multiple photoprotective systems were disrupted in cytokinin-deficient plants, demonstrating that the hormone is required for plants to survive under conditions of extreme light stress. *Arabidopsis histidine kinases 3* (*AHK3*) and, to a lesser degree, *AHK2*, and the type-B RRs, *Arabidopsis Response Regulators1* (*ARR1*) and *ARR12* were shown to be involved in the regulation of cytokinin activity (Cortleven et al., 2014). Additional evidence supports a protective role for cytokinin in the photosynthetic machinery under conditions of intense light (Cortleven and Schmülling, 2015). For example, cytokinin increases the antioxidant-based

protection in chloroplasts, leading to an increase in the chloroplast's lifespan (Procházková et al., 2008). Furthermore, because of the activation of the *PSARK::IPT* gene, drought-stressed transgenic *N. tabacum* plants produced more CK and enhanced CO_2 respiration, indicating that photosynthetic activities were well protected (Rivero et al., 2009). In comparison, another study reported that inhibiting cytokinin signaling in *A. thaliana* by mutating the *AHK2* and *AHK3* receptor genes showed an increased photooxidative stress tolerance under water deficiency circumstances (Danilova et al., 2014).

In addition, plants that have evolved unique response systems may be severely affected by a lack of light. In *A. thaliana* and *N. tabacum*, cytokinin is a key xylem-borne signal for photosynthetic adaptation to canopy light gradients (Boonman et al., 2009). Shade avoidance response is induced by low light, and it is characterized by the stimulation of elongation growth toward the light and the halt the growth of leaf in response. The shade-dependent auxin-induced degradation of cytokinin in developing leaf primordia is reliant on the *CKX6* gene, which has been discovered to be crucial. An increase in cytokinin degradation slowed leaf primordia development, saving resources for hypocotyl extension growth (Carabelli et al., 2007).

Light has the ability to transmit information about the time of day and to control the circadian clock. A prolonged light period has recently been revealed to generate stress symptoms in *A. thaliana* plants during the following night, a condition known as photoperiod stress (Nitschke et al., 2016; Nitschke et al., 2017). Plants suffering from cytokinin deficiency were the first to exhibit this phenotype, which could be described as following a standard sequence of events. An extended light period resulted in the induction of stress marker genes such as *BAP1* and *ZAT12*. Moreover, there is a significant increase in JA level several hours after the start of the night; the next day, a significant reduction in PSII maximum quantum efficiency (Fv/Fm) resulted in visible lesion formation in the leaves. When compared to cytokinin-deficient plants, WT plants displayed a considerably milder stress response, demonstrating that cytokinin plays a protective role. Cytokinin works primarily through *AHK3, ARR2*, *ARR10*, and *ARR12* and RRBs. After photoperiodic stress, several clock mutants (e.g., *cca1 lhy*) exhibited a significant stress response. Furthermore, stress sensitive clock mutants and cytokinin deficient plants shared a decreased expression or dysfunction of LHY and CCA1, two critical regulators of the circadian clock, indicating that a working clock is required to deal with photoperiod stress. Despite the fact that this novel kind of abiotic stress is ceased in natural settings, it is instructive regarding linkages between cytokinin and stress pathways that have hitherto gone unreported in the scientific community. It remains to be discovered what these "mechanical linkages" natural functions are.

Cold stress

As a result of the membrane system hardening in low temperatures, cells become more vulnerable (Liu et al., 2016; Prerostova et al., 2021). Cold stress causes a number of physiological changes, including loss of membrane integrity, an imbalance between water and nutrients, and an increase in ion outflow. Cold stress triggers transcriptional and post-transcriptional regulatory processes that may be Abscisic acid (ABA) dependent or ABA independent (Prerostova et al., 2021). Low temperatures lead to the accumulation of ROS as the antioxidant enzyme activity is reduced which results in the failure of the proper functioning of the ROS scavenging system. As a result, an excessive accumulation of ROS will have harmful effects on the cell membrane, resulting in cell metabolism disorder and ion leakage (Sui, 2015). Additionally, low temperatures impair reproductive development. Cold stress during the flowering period of *O. sativa*, for example, will induce sterility and yield loss (Feng et al., 2014; Wang et al., 2017). Furthermore, when the temperature falls below 0°C, freezing stress develops, and the ice crystals formed leads to mechanical damage and metabolic dysfunction in plants (Liu et al., 2013; Cheng et al., 2014).

The effects of cold stress on energy generation and biochemical demand are profound (Koc et al., 2018). As a result, Zoysiagrass (*Zoysia japonica*) in high latitudes (relatively low-temperature regions) is more frost-resistant than Zoysia grass (*Z. japonica*) at low latitudes (relatively high-temperature areas). This might be because of the larger carbohydrate content employed as an energy store, as well as the involvement of phytohormones in controlling plant adaptation to cold temperatures (Li et al., 2018). *Carpobrotus edulis* produces more cytokinin under low-temperature stress, and an Arabidopsis mutant *amp1* with greater cytokinin concentrations displayed a higher relative growth rate and greater plant yield than WT (Xia et al., 2008; Khan et al., 2017; Fenollosa et al., 2018). Simultaneously, overexpression of *AtCOR15a:ipt* in *Saccharum officinarum* (sugarcane) increases cold tolerance by delaying leaf senescence and minimizing membrane damage, preventing significant production loss and freezing injury (Belintani et al., 2012).

Numerous studies have employed cytokinins to increase plant response to low-temperature stress. The multi-step phosphorylation mechanism is now the focus of research on the link between cytokinins and low-temperature resistance. According to some research, A-type *ARRs* such as *ARR5*, *ARR7*, and *ARR15* are positive regulators of *A. thaliana* cold tolerance (Shi et al., 2012). The C-type ARR *ARR22* contributes to low-temperature resistance in plants by keeping the membrane in a normal condition (Kang et al., 2013). When compared to the WT, B-type *arr1* mutant is more susceptible to low temperatures and has lower cold resistance, but *A. thaliana* with B-type ARR1 overexpression has higher cold resistance,

suggesting that *ARR1* is a positive effector of cold signal transmission (Jeon et al., 2013). An *AHK2* or *AHK3* sends low-temperature signals to *ARR1* through *Arabidopsis histidine phosphotransfer proteins 2* (*AHP2*), *AHP3*, or *AHP5*, which shows that *AHP2*, *AHP3*, and *AHP5* plays an important function in upregulating tolerance to low-temperature stress (Jeon et al., 2013).

Plants low-temperature tolerance is further influenced by other cytokinin response factors (CRFs), which are discovered downstream of the cytokinin signaling cascade. Recent studies by Zwack et al. (2016) showed that *CRF4* is a positive regulator for the increased cold tolerance in *A. thaliana* with a *CRF4* mutation under low-temperature stress. An adaptation mechanism under cold stress may be triggered by high levels of *CRF2* and *CRF3* expression, which may stimulate lateral root development and overcomes the inhibition of cold-induced root growth, thereby increasing the plant's ability to withstand low temperatures (Jeon et al., 2016). As a result, Arabidopsis with mutations in *AHK2*, *AHK3*, *AHK4* (cytokinin receptor histidine kinases) and *ARR7* (an A-type ARR) exhibits enhanced low-temperature tolerance, suggesting a function for these cytokinin receptor histidine kinases in cold stress signaling (Jeon et al., 2010). However, more experimental validation is required. Increased cytokinin levels, whether exogenous or endogenous, may enhance resilience to cold temperatures (Belintani et al., 2012; Jeon et al., 2016). Exogenous cytokinin pre-treatment may increase the cold tolerance of *Triticum aestivum* (wheat) seedlings exposed to cold stress by boosting endogenous cytokinin levels in the leaves (Veselova et al., 2005). Under cold stress, the administration of exogenous cytokinin in the *ahk* mutant is comparable to the higher-order mutation of AHK (a negative regulatory factor), which may increase plant cold tolerance. The molecular processes, on the other hand, remain a mystery Exogenous cytokinin treatment of wild-type plants has been shown to improve their ability to withstand cold stress. Furthermore, it has been claimed that certain A-type *ARRs* are positive regulators of the genes that control the response to cold stress. (Jeon et al., 2010). Type-A *ARRs* are extensively expressed in transgenic plants due to ARR protein stabilization (Shi et al., 2012).

When exposed to cold stress, the hormones ethylene (ETH) and cytokinin act antagonistically. The C-repeat binding factor/DRE binding factor (CBF/DREB) transcription regulation cascade is the most well-known cold signaling mechanism. An increase in cold sensitivity may be achieved by overexpressing CBF (Gilmour et al., 2000). ETH has been shown to negatively regulate the cold signal by regulating the expression of CBFs and A-type *ARRs* genes. Moreover, A-type ARRs are believed to be essential for integrating cytokinin and ethylene signals in regulating plant response to cold stress, and CBFs have been shown to negatively regulate the cold signal by modulating the expression of CBFs and A-type *ARRs* genes (Shi et al., 2012). The cytokinin signaling pathway or cytokinin-related transcription factors may be implicated in the response to cold, according to these studies.

Heat stress

Heat stress damage the biological components by the production of ROS and proteins denaturation. It also has a detrimental impact on photosynthetic capability, resulting in a metabolic imbalance. The accumulation of heat shock proteins (HSP), which operate as molecular chaperones to prevent protein denaturation and aggregation, is one of the plant's defence strategies against heat stress (Mittler et al., 2011). Heat stress decreases cytokinin levels, and exogenous cytokinin treatment usually improves heat stress resistance (Hare et al., 1997). In *Nicotiana tabacum* and *Agrostis stolonifera* (creeping bentgrass), for example, exogenous application of cytokinin and increased endogenous cytokinin concentrations reduced the inhibitory impact of heat stress on chloroplast and photosynthesis growth, increased antioxidant system activity, and upregulated heat shock proteins (Liu and Huang, 2002; Veerasamy et al., 2007; Xu et al., 2009; Xu et al., 2010). In *Oryza sativa*, *Zea mays*, and *Passiflora edulis* (passion fruit), cytokinin treatment improved thermotolerance of reproductive tissue and increase the yield of these plants, indicating that cytokinin is capable of priming heat stress defense (Sobol et al., 2014; Wu et al., 2016; Wu et al., 2017).

Photosynthetic capability is negatively impacted by heat stress, which affects chlorophyll concentration and photochemical efficiency (Fv/Fm) of leaves. Additionally, heat exposure increases ROS generation and protease activity, resulting in leaf senescence (Hu et al., 2020). Endogenous cytokinin levels in *A. thaliana* increase in response to heat stress, especially in the leaves, resulting in higher cytokinin concentration is essential for greater heat tolerance (Skalak et al., 2016). Furthermore, heat stress stimulates the generation of ROS, and higher cytokinin levels may activate the antioxidant system to eliminate ROS (Xu et al., 2009). Furthermore, hormone, proteome, and transcriptome study further reveal that cytokinin plays a critical role in plant tolerance to heat stress, with the majority of heat shock (HS) response proteins being elevated in response to higher cytokinin levels (Skalak et al., 2016). Under heat stress, however, when the cytokinin signaling pathway is disrupted and/or the concentration of endogenous cytokinin is decreased in Arabidopsis seedlings, the elongation of hypocotyls is significantly and continuously inhibited, both during the initial heat stress and during the subsequent seedling growth. The increase of endogenous cytokinins may preserve normal plant development under high-temperature stress and have a favourable effect on plants that have been treated with heat shock (Skalak et al., 2016). As a result,

elevated levels of endogenous cytokinin may increase plant heat stress tolerance.

Introducing *isopentenyl transferase* (*IPT*) into *A. thaliana* seedlings boost endogenous cytokinin levels and hence increase tolerance to high temperatures (Skalak et al., 2016). As a result, boosting the amount of endogenous cytokinin in plants may help them to better withstand heat stress conditions. According to Skalak et al. (2016), the duration of elevated cytokinin levels is crucial for plant heat tolerance. The overexpression of the *IPT* gene under the start of continuous induction of expression promoters, such as the *HSP18* promoter or the senescence-activated promoter (*SAG12*), may be used to maintain high amounts of cytokinin. According to Xu et al. (2009), under heat stress, the overexpression of *SAG12:ipt* in *A. stolonifera* maintained the development and elongation of root systems, reduced chlorophyll loss and delayed leaf senescence, boosting plant heat tolerance. Subsequently, Xu et al. (2010) demonstrated that the overexpression of *IPT* generated by two separate promoters (*HSP18:ipt* and *SAG12:ipt*) results in a considerable increase in heat stress proteins in plants, boosting the plants ability to resist high temperatures (Xu et al., 2010). The DEX (dexamethasone) promoter (transient expression promoter)-driven overexpression of the *IPT* gene in *A. thaliana* may results in opening of stomata and leaf transpiration stimulation, both of which are important in the early stages of the heat stress response (Skalak et al., 2016). Furthermore, plant transpiration may only reduce the immediate demand for cooling, but it cannot alleviate the long-term impacts of heat stress because of its low water content (Wu et al., 2017). Increasing transpiration may only reduce the immediate requirement for cooling and cannot relieve the long-term impacts of heat stress owing to plants limited water content.

Along with boosting endogenous cytokinin content by *IPT* overexpression, a high level of cytokinin may be maintained by inhibiting endogenous cytokinin breakdown. Endogenous cytokinin breakdown may be inhibited in two ways. One of the methods is the mutation of the cytokinin oxidase/dehydrogenase (CKX) gene, while the other is through the use of cytokinin degradation inhibitors spray to decrease the activity of cytokinin oxidase/dehydrogenase (a negative regulator of cytokinin production). The CKX gene mutation causes an increase in cytokinin levels and grain production in *O. sativa*. Furthermore, in heat-sensitive *O. sativa* cultivars, CKX activity rises dramatically, resulting in poor cytokinin levels and yield. But the heat-resistant *O. sativa* CKX enzyme activity remains consistent, and the plants heat resistance improves (Wu et al., 2017). The CKX inhibitor INCYDE (cytokinin degradation inhibitor) is quite effective. The application of INCYDE boosts *A. thaliana* roots active cytokinin levels when exposed to heat stress (Zatloukal et al., 2008). On the other hand, Prerostova et al. (2020) have successfully demonstrated the opposite finding, that a single INCYDE treatment under heat stress had a detrimental influence on plant heat tolerance. The use of INCYDE in conjunction with acclimating plants may partially enhance *A. thaliana* heat resistance. Cytokinin response factors (CRFs) are thought to be a transcription factor that is linked to cytokinin. Under heat stress, *CRF1* expression in *Solanum lycopersicum* (tomato) roots is drastically reduced (Shi et al., 2014). Accordingly, we conclude that CRFs play a significant part in the plants heat stress signal pathway and that more study is required to elucidate the underlying process.

Moreover, exogenous cytokinin performs a similar effect to endogenous cytokinin when exposed to heat stress. Exogenous cytokinin zeatin ribose (ZR) treatment improves *A. stolonifera* heat tolerance by reducing root mortality, increasing the antioxidant system activity, maintaining a higher chlorophyll content, and upregulating related heat shock proteins (Veerasamy et al., 2007; Xu et al., 2010; Hu et al., 2020). To further boost plant growth and production, exogenous cytokinin has been implemented to enhance the heat stress tolerance of reproductive organs in plants.

Salt stress

Salt stress affects numerous biochemical and physiological processes in plants. Accumulation of sodium ions (Na^+) in plants may disrupt ion homeostasis, imbalance the potassium ion (K^+)/Na^+ ratio, and Na^+ ion toxicity, all of which can result in secondary stress, including oxidative stress (Feng et al., 2015; Song et al., 2015; Liu et al., 2017; Guo et al., 2018). Moreover, ion leakage, cell membrane damage, and direct damage to proteins and other macromolecules are all caused by oxidative stress, which may result in cytotoxicity, membrane malfunction, and cell death in certain cases (Lin et al., 2018; Liu et al., 2018). Leaf senescence will be accelerated upon ion stress and oxidative stress, which will destroy the chlorophyll, limit photosynthesis and lower the yield (Han et al., 2011; Li et al., 2012; Liu et al., 2017). According to several research, the deleterious effects of salt stress on plants such as *Raphanus sativus* (radish) and *N. tabacum* are connected to cytokinins (Vankova et al., 2010). Under salinity stress, however, the alterations in endogenous cytokinins in various plants are not homogeneous. Due to the variability in cytokinin concentration under salt stress, there is no one-size-fits-all strategy for increasing plant salt tolerance via exogenous and endogenous cytokinin manipulation.

According to recent research, the cytokinin level of *Malus domestica* (apple) rootstock 'robusta' and *Solanum lycopersicum* seedlings remains high under salinity stress (Keshishian et al., 2018; Feng et al., 2019). Additionally, *A. thaliana*, *O. sativa*, and other plants exhibit an increase in cytokinin levels in response to salt stress (Prerostova et al., 2017; Joshi et al., 2018). The upregulation of cytokinin in certain plants may aid in the recovery from salt stress. Due to cytokinin accumulation, the *OsCKX2* knockout rice mutant exhibits a greater relative water content and yield under salinity stress than the WT, enhancing

salt tolerance (Joshi et al., 2018). Moreover, increased plant resistance to salt stress may be achieved by increasing the activity of antioxidant enzymes by spraying INCYDE on S. lycopersicum. (Aremu et al., 2014). Avalbaev et al. (2016) showed that *Triticum aestivum* pre-treated with methyl jasmonate (MeJA) can maintain a high concentration of cytokinin by lowering the level of CKX transcription that is caused by salt stress, thereby delaying the negative impact of salt on seedling growth, and enhance salt resistance (Avalbaev et al., 2016). In response to the deletion of 42 bp from the promoter region of *IPT5* gene, the expression level and cytokinin content of *M. domestica* rootstock "robusta" under salinaty stress were both increased, with the latter remaining at a high level and exhibiting greater tolerance to salt stress (Feng et al., 2019). *SlIPT3* overexpression makes *S. lycopersicum* more salt-tolerant by keeping their photosynthetic pigment and K^+/Na^+ ratio high, which means they can withstand more salt than the WT plants (Ghanem et al., 2011).

High cytokinin concentration, on the other hand, have been demonstrated in experiments to reduce plant salinity tolerance. Furthermore, overexpression of *AtIPT8* in *A. thaliana*, which has a high cytokinin level, results in a substantial reduction in the survival rate of plants under salt stress. This is due to the downregulation of stress-responsive genes, the inhibition of the antioxidant system, and the reduction of chlorophyll content in the plants (Wang et al., 2015). Furthermore, plants with lower cytokinin levels have been reported to be more resistant to abiotic challenges, such as salt stress, owing to decreased cytokinin production or increase degradation (Ghanem et al., 2011; Avalbaev et al., 2016; Zhang et al., 2018). In comparison to the wild type, salt tolerance is higher in cytokinin synthesis pathway mutants with loss-of-function mutations, such as *Atipt1*, *Atipt3*, *Atip5*, and *Atipt7* (Nishiyama et al., 2012; Zhang et al., 2018). In the moss *Physcomitrella patens*, overexpression of *PpCKX1* lowers cytokinin levels and increases salt tolerance (Hyoung et al., 2019). Salt tolerance in transgenic *Medicago sativa* (alfalfa) plants is improved by overexpression of *MsCKX*, which maintains a high K^+/Na^+ ratio and increases the activity of antioxidant enzymes to scavenge ROS (Li et al., 2019). These CKX-induced cytokinin-deficient plants are more valuable for deciphering the function of cytokinin than *ipt* mutants (Werner et al., 2003).

Plant salt tolerance is also influenced by components in the cytokinin signaling system. The cytokinin receptor *AHK1* is a positive regulator of salt stress response and plays an active regulatory function in osmotic stress signaling (Tran et al., 2007). Furthermore, plant tolerance to salt is improved by *ahk2*, *ahk3*, and *cre1* mutants, which upregulate the expression of homologous stress response genes, indicating that these members have a negative regulatory function in salt tolerance (Tran et al., 2007). By promoting the expression of *A. thaliana high-affinity K^+ transporter 1;1* (*AtHKT1;1*) in the roots, the *arr1* and *arr12* mutants decrease sodium accumulation in the aerial portions and improve salinity stress tolerance (Mason et al., 2010). Overexpression of *ARGONAUTE2* (*AGO2*) in *O. sativa* decreased cytokinin concentration in shoots and increase cytokinin level in roots, resulting in higher salt tolerance and grain length in *O. sativa* under salt stress, according to Yin et al. (2020). In addition, by boosting the production of *BIG3* (*GRAIN3*), which encodes a protein that may be involved in cytokinin transport, and AGO2, which changes the histone methylation level of BG3, AGO2 impacts the distribution of cytokinin. CRFs are thought to be downstream signaling molecules for RRs in certain instances (Hallmark et al., 2019). Consequently, under salt stress, RNAi silencing of *ThCRF1* reduced salt tolerance in *Tamarix chinensis* (halophyte: salt-tolerant plants), while overexpression of *ThCRF1* greatly increased salt tolerance in the halophyte through regulating osmotic potential and increasing antioxidant enzyme activity (Qin et al., 2017).

Depending on the plant species and the degree and duration of salt stress, increase or downregulation of cytokinin improves salt tolerance. Exogenous cytokinin treatment has a range of impacts on tolerance of salt stress in plants of different species. Although pre-treatment of legumes with exogenous cytokinins increases their susceptibility to salt, most research has shown that exogenous cytokinins improve plant salt tolerance, particularly in cereal crops like *O. sativa* and *T. aestivum* (Iqbal et al., 2006; Javid et al., 2011). By efficiently relieving salt-induced leaf senescence and other forms of physiological or developmental damage, foliar application of 6-Benzylaminopurine (6-BA; synthetic cytokinin) improves *Solanum melongena* (eggplant) and *Lolium perenne* (perennial ryegrass) salt resistance (Wu et al., 2014; Ma et al., 2016). These findings suggested that we can spray exogenous cytokinins onto plants to improve salt resistance.

Drought stress

Reduced photosynthesis, decreased crop yields, and accelerated senescence is some of the negative consequences that drought stress may have on plant physiological activities (Liu et al., 2012; Zheng et al., 2017; Hai et al., 2020). Subsequently to salt stress, the likelihood of increasing plant drought resistance via cytokinin regulation is dependent on the stress duration, plant dehydration rate and soil water potential, (Veselov et al., 2017). Furthermore, endogenous cytokinin upregulation and downregulation have both been reported to increase drought tolerance. (Werner et al., 2010; Zhang et al., 2018). According to several research, under drought stress, plant endogenous cytokinins accumulation is decreased, and this leads to improving plant drought tolerance through a variety of physiological responses such as early leaf senescence, leaf abscission and stomatal closure (Xu et al., 2016; Naidoo and Naidoo 2018; Calvo-Polanco et al., 2019). Moreover, cytokinin is a negative regulator of plant root development and branching,

enhancing cytokinin breakdown in the root may result in plants with an improved root-to-shoot ratio, larger root system, and long-term drought resistance (Pospisilova et al., 2016; Ramireddy et al., 2018).

Overexpression of CKX causes cytokinin to be downregulated, resulting in slower plant development and higher protective chemical content (proline, betaine, etc.) as well as drought resistance in *A. thaliana*, *N. tabacum*, *Cicer arietinum* (chickpea), and *Hordeum vulgare* (barley) (Werner et al., 2010; Nishiyama et al., 2011; Pospisilova et al., 2016; Ramireddy et al., 2018; Khandal et al., 2020). In *A. thaliana*, the *ipt1*, *3*, *5*, and *7* mutants had lower endogenous cytokinin content and improved drought tolerance (Nishiyama et al., 2011). Reduced levels of cytokinin cause roots to expand and shoot to have a higher root-to-shoot ratio, which improves root surface area available for water absorption. Smaller branches and leaf areas in comparison to roots may significantly reduce transpiration which further improves the tolerance (Werner et al., 2010; Lubovská et al., 2014; Prerostova et al., 2018). Accordingly, the whole plant can keep a relatively high relative water content and become more drought-resistant. Furthermore, by counteracting the effects of the oxidase system, downregulation of cytokinin may contribute to an improvement in drought tolerance (Lubovská et al., 2014). Conventional multi-step phosphorylation system in plants, including RRs, HKs, and HPs, is responsible for cytokinin signaling in the plant. Cytokinin signaling is also regarded to be a negative regulator of drought resistance because *ahk2*, *3*, *5*, *arr1*, *10*, and *12* display a significant drought-tolerance phenotype (Kang et al., 2012; Nguyen et al., 2016). Since the cytokinin signal suppresses stress response gene expression, it is hypothesized that decreasing the amount of cytokinin in the plant might enhance plant survival under challenging environmental conditions (Zhang et al., 2018). Moreover, it was shown that the expression of *SlCRF1*, *SlCRF2*, *SlCRF3*, and *SlCRF5* was regulated throughout the drought and recovery phase in *Solanum lycopersicum* plants, demonstrating that CRFs respond to drought stress and providing a novel idea for improving plant resistance to drought stress (Gupta et al., 2014; Shi et al., 2014).

Drought, salt, and cold stress all results in reduce water availability, resulting in physiological reactions that overlap. Different strategies have been developed in plants to optimize the use of water, including redirection of root development, change of cell membrane characteristics, and control of transpiration via stomata (Feng et al., 2016; Zhu, 2016). Moreover, drought response is tightly linked to the activity of abscisic acid (ABA), which increases in response to drought stress and binds to its corresponding receptor family PYRABACTIN RESISTANCE1 (PYR1)/PYR1LIKE (PYL)/ ABA RECEPTOR REGULATORY COMPONENTS (RCAR). An enzyme called PROTEIN PHOSPHATASES 2C (PP2c) is inhibited by the ABA-PYR/PYL complex. When ABA is absent PP2c dephosphorylate and keeps subclass III SUCROSE NONFERMENTING1 (SNF1)–RELATED PROTEIN KINASES2 (SnRK2s) inactive. Furthermore, SnRK2s that have been activated phosphorylate transcription factors known as ABRE BINDING FACTOR (ABFs)/ABSCISIC ACIDRESPONSIVE ELEMENT (ABRE) BINDING PROTEINS (AREBs), which control the expression of target genes to promote plant drought tolerance (Miyakawa et al., 2013; Joshi et al., 2016). Moreover, drought and osmotic stress activate another signaling pathway that is independent of ABA and includes GROWTH REGULATING FACTOR7 (Kim et al., 2012).

Drought reduces cytokinin levels in *A. thaliana* and *Glycine max* (soybean) by repressing *IPT* genes and upregulating *CKX* genes (Guo and Gan, 2011; Nishiyama et al., 2011; Le et al., 2012; Nishiyama et al., 2013; Ramireddy et al., 2014; Nguyen et al., 2016; Todaka et al., 2017). Moreover, genetic studies in *A. thaliana* have consistently shown that cytokinin functions as a negative regulator of drought stress tolerance, which is consistent with previous findings (Nishiyama et al., 2011; Nishiyama et al., 2013; Nguyen et al., 2016). Furthermore, lowered cytokinin levels and signaling resulted in at least two primary effects: greater sensitivity to ABA, establishing cytokinin as an ABA antagonist and a decrease in shoot growth, which is an adaptive response to drought (Werner et al., 2003; Riefler et al., 2006). Numerous components of the cytokinin signalling that are functionally significant in the tolerance to drought stress have been established (Li et al., 2016). Therefore, plants with mutant cytokinin receptor genes (*AHK2* and *AHK3*), HPT genes (*AHP2*, *AHP3*, and *AHP5*), or RRB genes (*ARR1*, *ARR10*, and *ARR12*) exhibited greater drought stress tolerance compared to control plants (Nishiyama et al., 2011; Nguyen et al., 2016). However, drought tolerance was connected with a variety of physiological changes, including an increase in cell membrane integrity, reduction in stomatal aperture, and an increase in ABA sensitivity (Nguyen et al., 2016). According to a transcriptomic study, cytokinin regulates a large number of dehydration/ drought and/or ABA-responsive genes involved in drought adaptation (Nguyen et al., 2016). Increasing evidence suggests that under drought and salt stress, the RRA genes *ARR5*, *ARR6*, *ARR7*, *ARR15*, and *ARR22*, which also react to cold stress in a cytokinin independent manner, were upregulated, showing a partial overlap of the response pathways (Kang et al., 2012; Jeon and Kim, 2013). Drought resistance is increased in plants that overexpress *ARR22* (Kang et al., 2013). *A. thaliana* has a *MYB2* gene, which is activated by the ABA, which suppresses the *IPT* genes and lowers the level of cytokinin (Guo and Gan, 2011). In turn, this reduces the output of the AHK/AHP/ARR signalling cascade that aids the plants adaptation to drought and osmotic stress.

The interaction between SnRK2s, RRAs, and RRBs is another connection. The RRBs *ARR1*, *ARR11*, and *ARR12* physically engage with SnRK2s in non-stress situations, repressing their

kinase activity and shutting off the drought response pathway. Furthermore, in drought-stressed plants, SnRK2s phosphorylate the *RRA ARR5*, inhibiting cytokinin signaling and limiting plant growth. These interactions demonstrate cytokinin regulates growth-trade-offs is well understood.

Interactions of cytokinin with other phytohormones under abiotic stresses

Plant responses to abiotic stress conditions are mostly based on interactions among hormone signals. Cytokinin participates in a complex signal network with other phytohormone signaling pathways rather than playing a separate regulatory function. Cytokinin does not have a regulatory function that is independent of other phytohormone signaling pathways; rather, it acts within a complex signal network that includes several pathways (Li et al., 2016). Furthermore, coordinating tissue expansion in response to environmental changes requires the interaction of other phytohormone. As a result, the plant is able to respond rapidly to its changing environment due to a network of tightly interlinked signaling systems.

Abscisic acid (ABA) regulates one of the earliest plant drought responses, stomata closure, which controls the trade-off between CO_2 intake and water loss via transpiration (Sah et al., 2016; Vishwakarma et al., 2017). Although ABA strongly interacts with cytokinins, it also regulates mid- and long-term plant responses to abiotic stress, including regulation of plant architecture. Accumulation of stress-induced ABA in turn downregulates cytokinin production by way of the MYB2 transcription factor (TF), alleviating the repression on multistep phosphorelay (MSP) and activating genes that are ABA- and stress-inducible (Li et al., 2016). Through the downregulation of shoot growth and the acceleration of root development, ABA-mediated suppression of cytokinin signaling starts the process of redesigning the plant body. This enables the plant to increase water intake from deeper soil layers while minimizing water loss (Li et al., 2016). Accordingly, ABA hypersensitivity and increased drought resistance are seen in MSP signaling mutants, such as those with defects in the cytokinin sensors AHK2, AHK3, and AHK4 and type-B ARRs ARR1, ARR10, and ARR16 (Tran et al., 2007; Tran et al., 2010; Nguyen et al., 2016). It has been demonstrated that ABA and drought may both downregulate the expression of *ARR1*, *ARR10*, and *ARR12* (Nguyen et al., 2016). According to Takatsuka and Umeda (2019), ABA also inhibits *ARR2* but not *AHK3* or *AHK4* and there may be a function for ABA in the regulation of AHP2's nucleocytoplasmic partitioning (Marchadier and Hetherington, 2014). Tran et al. (2007) found that the osmosensor AHK1 is not a negative regulator of the ABA-mediated stress response, but rather a positive regulator. This suggests that there may be some specificity at the level of signals that start the MSP-regulated (drought) stress response (Hai et al., 2020).

There are two ways in which ABA interferes with MSP activity: ABA-controlled downregulation of the generation of cytokines and the interaction between ABA signaling components and MSP. ABA-activated ABI4 binds promoters and downregulates *ARR6*, *ARR7*, and *ARR15*; arr4, arr6, arr7, and arr15 mutant lines are hypersensitive to ABA (Jeon et al., 2010; Wang et al., 2011). ARR5, a type-A ARR and negative regulator of MSP signaling, has numerous Ser residues that are phosphorylated by SnRK2.2, SnRK2.3, and SnRK2.6. By inhibiting cytokinin signaling, this results in stability of the ARR5 protein, which improves ABA responsiveness and drought tolerance.

Dautel et al. (2016) postulated an AHK2/AHK3-dependent phosphorylation of Thr6 and Tyr19 of KIN10, one of the two subunits of SnRK1, acting under energy stress in their phosphoproteomic analysis (Baena-González and Sheen, 2008). According to KIN10-based global gene regulation (Radchuk et al., 2006; Baena-González et al., 2007), SnRK1 down-regulation has previously been linked to cytokinin and auxin signaling. However, ethylene signaling was found to be negatively regulated by SnRK1 phosphorylation-mediated inactivation of EIN3 (Kim et al., 2017), leading to a growth. There is a bidirectional negative link between ABA and cytokinin levels/signaling. ABA insensitivity in seed germination was caused by the overexpression of cytokinin production via the upregulation of AtIPT8 (Wang et al., 2011). In the process of seed germination, ABA insensitivity was caused by an increased cytokinin production brought about by an overexpression of *AtIPT8*. Additionally, ABA was unable to inhibit the expression of the type-A ARRs ARR4, ARR5, and ARR6 that physically interact with ABI5 and reduce *ABI5* levels when endogenous cytokinin levels are increased (Wang et al., 2011). The cytokinin-responsive type-B ARRs ARR1, ARR11, and ARR12 that physically engage with SnRK2s and suppress the kinase activity of SnRK2.6 are most likely the cause of the decreased sensitivity to ABA under high endogenous cytokinin levels. The cytokinin-dependent control of ABA signaling may be regulated at the transcriptional level by ARR10, which was shown to bind the promoters of multiple ABA signaling genes (Zubo et al., 2017).

Cytokinins suppress expression of the Arabidopsis HIGH-AFFINITY K + TRANSPORTER 1; 1 (AtHKT1; 1), which is responsible for removing sodium ions from root xylem, in response to salt stress through ARR1 and ARR12. This transporter is responsible for removing sodium ions. Additionally, it was shown that cytokinins controlled the type A response regulator ARR5's expression in response to salt stress mostly *via* ARR1 and ARR12, demonstrating the role of specific MSP components in the roots in regulating sodium accumulation in the shoots (Mason et al., 2010).

The hormonal network underpinning the intricacy of plant responses to stress is also influenced by the ethylene (ET) pathway. ET has been investigated in the contexts of development and stress (Vanstraelen and Benková, 2012; Beguerisse-Díaz et al., 2013; Zhai et al., 2013), and it has most recently been shown to play a negative regulatory role in cold tolerance (Shi et al., 2012). Interestingly, cold stimulates the expression of *ARR5*, *ARR6*, *ARR7*, and *ARR15* in a manner similar to dehydration, most likely to inhibit cytokinin signal transduction and growth (Jeon et al., 2010; Kang et al., 2012). According to the findings of Shi et al. (2012), ethylene biosynthesis and signaling adversely affects the cold stress response in Arabidopsis. This is accomplished via the repression of cold-inducible *C-REPEAT BINDING FACTORS* (*CBFs*) (*CBF1*, *CBF2*, and *CBF3* genes), and the type-A ARR genes *ARR5*, *ARR7*, and *ARR15*. This ethylene-induced suppression was expected to be mediated by direct binding of EIN3 to the promoters of type-A ARRs, so possibly suggesting another mechanistic connection between classical ethylene signaling and MSP during plant desiccation.

Despite the fact that ET disrupts the cytokinin signaling pathway's output, the pathway itself is also influenced by cytokinin. In fact, cytokinin is responsible for the stabilization of the enzymes 1-aminocyclopropane-1-carboxylate synthase 5 (ACS5) and ACS9 (Chae et al., 2003; Hansen et al., 2009), which are responsible for the conversion of S-adenosyl-methionine to 1-aminocyclopropane-1-carboxylic acid. This stability might result in an accumulation of ET, which would then have the potential to influence plant development processes such as root expansion (RůžiČka et al., 2007). According to Lehotai et al. (2012), the activation of both cytokinin and ET signaling in response to selenite-induced stress by means of the ARR5 and ACS8 markers and decrease in the levels of auxin suggests that the hormonal regulatory network that underlies stress responses is more complex than previously thought. Interestingly, there are tissue-specific characteristics in the cytokinin-ET and cytokinin-ABA interactions. Contrary to ET, which accumulates mostly in roots in response to high CK levels, CK treatments have been shown to enhance the accumulation of ABA in shoots but not in roots (Žďárská et al., 2013).

Priming as a strategy to develop abiotic stress tolerance

Cytokinin has been shown in the literature to be used as a priming agent to activate plant immune for biotic stress responses and biotrophic. Priming technology, on the other hand, is not widely used to protect plants from the negative effects of abiotic stressors or to prepare them to better withstand them. Moreover, it has been shown that priming the stress response pathways would be advantageous for the plant since it enables quicker and more robust responses with little energy expenditure. Although priming with several plant growth regulators (PGR) has been shown to be beneficial, evidence on employing cytokinins as priming agents is restricted to few experiments using kinetin or 6-benzylaminopurine (BAP). BAP has long been one of the cytokinins that is most often given to plants exogenously to dealyed senescence and decrease the impact of stress. Exogenous cytokinin treatment may reduce abiotic stressors on agricultural plants, resulting in enhanced growth, development, and yield. Similarly, cytokinin treatment lowers plant salinity stress (Ha et al., 2012) and promotes starch accumulation in salt-stressed rice plants (Javid et al., 2011).

Abiotic stress has been reduced in a variety of crop species by seed priming with cytokinins or a combination of cytokinins and other plant hormones. It is possible that genes associated to cytokinin play a significant role in the regulation of regeneration once a stress has been removed. Priming with cytokinins improves the production of chlorophyll (Chl) and the accumulation of biomass in plants. Additionally, it increases the photosynthetic rate, promotes membrane integrity, and keeps a stable ionic level. Wheat seeds primed with kinetin at concentrations of 100 mg L^{-1}, 150 mg L^{-1}, and 200 mg L^{-1} were shown to have improved germination and tolerance to salt. This was accomplished by lowering ABA concentrations and raising IAAs concentrations (Iqbal et al., 2006). Similar findings were made by Mangena (2020), who claimed that priming soybean seeds with cytokinins (Benzyl adenine; 4.87 mg L^{-1}) improved soybean root biomass, flowering, and fruiting under drought stress. *Arachis hypogaea* L. aged groundnut seeds were primed with cytokinins (150 ppm), which improved antioxidant enzyme activities and reduced oxidative damage to improve germination and seedling indices (Sepehri et al., 2016). In addition, the mode of action of these PGRs in enhancing seed and plant fitness through priming has not been investigated. Moreover, it has been reported that exogenous application of cytokinins reduces ABA-induced stomatal closure because this PGR, which are important for stomatal movement, are involved (Tanaka et al., 2006). However, the effects of seed priming with cytokinins on stomatal movement remain unknown.

Genetic engineering of cytokinin for improving or redesigning plant abiotic stress tolerance

Crop yield and production are threatened by abiotic factors such as severe temperatures, nutrient deficiency, low water levels, high salt concentrations and excessive light. Plants cytokinin mediated stress responses are highly dependent on the phytohormone concentrations (O'Brien and Benkova, 2013). Moreover, plants get acclimatized to stress as a result of both constitutive decrease and overproduction of cytokinins. As a result, precise manipulation will lead to altering its concentrations to achieve desired results (summarized in

Table 1) (Rivero et al., 2007; Werner et al., 2010; Nishiyama et al., 2011; Ha et al., 2012). *A. thaliana* the model plant, has been the subject of the most extensive study on cytokinin-mediated stress responses till date (Ha et al., 2012). The most common method for lowering cytokinin levels is to change the expression of the *CKX* or *IPT* genes. Subsequently, the overexpression of *CKX* genes, as well as the disruption of *IPT* genes, will result in a reduce cytokinin levels. Furthermore, plants with cytokinin deficiency show bushy root growth, diminished apical dominance, and stunted shoot developmental phenotype. Nishiyama et al. (2011) used gain and loss-of-function mutants to show that the Arabidopsis cytokinin-overexpressing plants (*35S:CKX1-35S:CKX4*) and *ipt1, 3, 5, 7* quadruple mutant were more salt and droughts -tolerant than WT plants. Furthermore, root growth assays and intracellular electrolyte leakage measurements suggested that cytokinin deficient plants were more resistant to salinity stress owing to increased primary root development and more tolerant to drought because of improved cell membrane integrity (Nishiyama et al., 2011). Additionally, the reduction in cytokinin levels shown in *AtCKX*-overexpressing Arabidopsis transgenic plants had a major influence on the growth and development of several tissues, including roots and shoots, reproductive organs, floral, and vascular development (Werner et al., 2003). Root-specific expression of *CKX* in *N. tabacum* using the *W6:CKX1* construct (expression of *CKX1* driven by a *WRKY6* promoter) and in *A. thaliana* using the *P10:CKX3* construct (expression of *CKX3* driven by a *PYK10* promoter) revealed an enlargement of the root system architecture (RSA) in the transgenic lines, which showed similarity to the root feature of plants grafted between *35S:CKX1* or *35S:CKX3* (Werner et al., 2010). Furthermore, the transgenic plants accumulated more minerals, such as calcium, phosphate, molybdenum, and magnesium when compared with the WT (Werner et al., 2010). These data collectively support that the root development improved plants tolerance to water stress and nutrient deficiency.

Constitutive overexpression of cytokinin gives rise to severe anomalies in biological processes such as organogenesis, cell division, meristematic activities, and gametophyte development (Kieber, 2002). Because of this, organ-specific and stress-inducible cytokinin synthesis is thought to be more desirable. Gain-of-function studies, for example, showed that using stress-inducible promoters alternative to constitutive promoters might prevent growth abnormalities associated with endogenous cytokinin overexpression, such as dwarf and limited root growth phenotypes, results in improved control of cytokinin biosynthesis (Xing et al., 2009; Peleg and Blumwald, 2011). Several promoters, such as *HSP* (*heat shock protein*), *PSARK* (*senescence-associated receptor-like kinase*), *PSAG12* (*senescence-associated genes12*), and *rd29A* (*response to dehydration 29A*), have been successfully used to drive conditional expression of the *Agrobacterium tumefaciens* mediated *IPT* gene in *A. thaliana* (Zhang et al., 2000), tobacco (*N. tabacum*) (Rivero et al., 2007; Rivero et al., 2010), creeping bentgrass (*Agrostis stolonifera*) (Merewitz et al., 2010), rice (*O. sativa*) (Peleg et al., 2011), peanut (*Arachis hypogaea*) (Qin et al., 2011), cotton (*Gossypium hirsutum*) (Kuppu et al., 2013), and cassava (*Manihot esculenta*) (Zhang P. et al., 2010), to increase tolerance to a variety of stresses, including waterlogging and drought (Figure 2). Transgenic plants with increased cytokinin exhibited better adaptive responses to numerous stresses with an improvement in photosynthesis capacity, transpiration rate, intracellular water content, and delayed leaf senescence, all of which shows the potential to be useful and economical in agriculture.

The promoter *PSAG12* deriving the expression of the *IPT* gene significantly delayed the onset of leaf senescence but resulted in an unexpected change in source-sink relationships, nitrogen (N) mobilization, reproduction and growth in response to water stress were also reported (Jordi et al., 2000). Thus, an alternate promoter, *PSARK*, has been frequently employed to overcome such a problem, since this promoter may activate *IPT* expression prior to the onset of leaf senescence (Rivero et al., 2007; Reguera et al., 2013). Similarly, *A. thaliana* stress-induced *rd29A* overexpressed the *IPT* gene to confer salinity stress tolerance in *N. tabacum* (Qiu et al., 2012). Salt tolerance in transgenic *G. hirsutum* was improved by overexpressing the *A. tumefaciens IPT* gene using the *Ghcysp* (*G. hirsutum* cysteine proteinase) promoter, which is from the same family of cysteine endopeptidase genes as *SAG12* (Liu et al., 2012). Furthermore, when drought stress occurs during the vegetative stage of the *G. hirsutum* plant, this strategy proved efficient in enhancing plant performance, but drought stress after the flowering stage failed to provide a yield advantage (Zhu et al., 2018). Early flowering and a later heading date were caused by *PSAG39:IPT* expression in *O. sativa*. Under drought conditions, this was expected to assist plants to deal with modest water restrictions and increase grain yields (Zou et al., 2007; Liu et al., 2010). Additionally, increased *IPT* expression assisted the plants survival ability under stressful events and at the recovery stage under waterlogging and submerging situations (Huynh et al., 2005).

Heavy metal stress (HMs) has a negative impact on plant metabolic processes, particularly when zinc concentrations are elevated (Gill, 2014). When compared to WT, *PSAG12:IPT* transgenic *N. tabacum* displayed stronger protection against high zinc contamination by reducing transpiration rates and net photosynthetic while retaining free amino acids synthesis, which is suggestive of appropriate nitrogen (N) metabolism (Pavlíková et al., 2014). Furthermore, a lack of nutrients, particularly important minerals like N, may cause massive self-destructive processes within plant cells. *N. tabacum* transformed with the *PSARK::IPT* construct might aid in the inhibition of ROS (reactive oxygen species) formation and prevent the detrimental effects on plants induced by decreasing the N concentration (Rubio-Wilhelmi et al., 2011).

Subsequently, another study employed the P*SAG12*:*IPT* construct to produce transgenic *A. stolonifera* that improved plant survival in the face of N or phosphate (P) deprivation (Zhang Y. et al., 2010).

Overexpression of *A. tumefaciens IPT* gene to increase endogenous cytokinins level as a countermeasure against adversarial temperature has also been implicated in many species, such as generating low temperature-tolerant sugarcane (*Saccharum* spp.) and cold-resistant tall fescue (*Festuca arundinacea*) using the Arabidopsis *COR15a* (cold-regulated gene15a) promoter and the maize ubiquitin promoter, respectively (Hu et al., 2005; Belintani et al., 2012). In response to heat stress, an effort was made on *A. stolonifera* utilizing HSP and PSAG12 promoters to overexpress the *IPT* gene from *A. tumefaciens* (Xing et al., 2009; Xu et al., 2009). Furthermore, Xing et al. (2009) have also established that *SAG12-ipt-* and *HSP18-ipt* bearing transgenic *A. stolonifera* exhibited significantly longer leaf life-span when compared to WT when subjected to dark and heat treatment, respectively. Another *A. thaliana* SAG family promoter, *SAG13*, may induce *IPT* expression in all mature leaves before senescence, similar to PSARK expression pattern, but with a more severe altered source-sink relationship (Swartzberg et al., 2006). Under salt stress, a modified strategy of employing root-specific cytokinin overproduction under the direction of a constitutive promoter might help *Solanum lycopersicum* (tomato) plants increase plant growth and yield (Ghanem et al., 2011). In salt-treated *S. lycopersicum* plants, root-to-shoot cytokinin transport was significantly boosted, resulting in better ion homeostasis, vegetative growth, delayed leaf senescence (in plants with root-specific *HSP70*:*IPT* expression), and increased fruit yield (Ghanem et al., 2011). Thus, this research proposed a unique effective technique to reduce salt-induced agricultural yield constraints.

Transiently increasing the cytokinin level *via* the crucial distance between the gene and its promoter is another application of the genetic engineering method. By utilizing the constitutive 35S promoter the *A. tumefaciens IPT* gene was fused to the downstream of other genes, like *AtGolS2* (Arabidopsis galactinol synthase) or *AOC* (*Bruguiera sexangula* allene oxide cyclase), which were involved in cold and salt stress tolerance, respectively (Guo et al., 2010). Subsequently, *A. thaliana* transgenic plants carrying the *pVKH35S-AOC-ipt* and *pVKH35S-AtGolS2-ipt* genes were able to achieve a small rise in cytokinin levels, resulting in improved plant development, higher chlorophyll production, and longer flowering (Guo et al., 2010). Another method of transiently increasing cytokinin activity is to modify the expression of O-glycosyltransferase moderately. In response to the successful isolation of the *ZOG1* (*Zeatin O-glucosyltransferase*) gene from the *Phaseolus lunatus* plant, which codes for the ZOG protein, transgenic *N. tabacum* expressing *35S:ZOG1* and *SAG12:ZOG1* transgenes were developed (Martin et al., 1999; Marie et al., 2008). Therefore, the stress-induced elevation in calcium levels aided the *SAG12:ZOG1*-transformed plants in establishing growth more quickly than the WT plants at the post-drought recovery stage, as compared to the WT plants. In contrast, transgenic plants that had the *35S:ZOG1* construct had a slower recovery rate, which suggests that having more cytokinin in the plant before a long and severe drought period could have a negative effect (Marie et al., 2008).

Conditionally or locally boosted cytokinin synthesis has been shown to improve plant growth and yield in *Brassica napus* (canola) and *A. stolonifera* utilizing various promoter and *IPT* gene combinations (Kant et al., 2015; Xu et al., 2016). In the field, yields of IPT transgenic *B. napus* were higher in both stressed and non-stressed conditions (Kant et al., 2015). The information that cytokinin is a negative regulator of elongation development of the main root and root branching has been used to develop another engineering strategy to increase tolerance to drought in plants (Werner et al., 2003). *A. thaliana*, *N. tabacum* and *Hordeum vulgare* roots had lowered cytokinin levels when *CKX* genes were only expressed in the roots. This led to a larger root system with mostly unaltered shoot growth and development (Werner et al., 2010; Macková et al., 2013; Ramireddy et al., 2018). A greater survival rate of *CKX* transgenic *N. tabacum* plants under drought stress in an intermixed planting revealed that these plants were more effective in competing for limited water resources than WT tobacco plants (Werner et al., 2010). Increased cytokinin degradation in the roots of transgenic *H. vulgare* (barley) resulted in a reduced stress response to long-term drought conditions which includes increased stomatal conductance and CO_2 assimilation rates, decreased activation of critical ABA metabolism genes, and decreased build-up of ABA (Ramireddy et al., 2018). While large soil volume explored by *CKX* transgenic plants has been linked to some of these favourable benefits, other mechanisms, such as interplay between the cytokinin and ABA signalling pathways, may also be responsible for the altered response to drought stress in these plants (Vojta et al., 2016; Ramireddy et al., 2018).

Cytokinin related gene applications in genetic engineering have shown considerable promise for stress tolerance, leading to sustainable agriculture, however, they are primarily overexpressed research. Therefore, genetic engineering and breeding strategies leads to increase abiotic stress resistance by manipulating these genes. Although these molecular players have been extensively examined in non-crop plants such as *A. thaliana* and *N. tabacum*, they have yet to be investigated in agronomically important crops. Thus, the mechanism governing cytokinin signaling in economically significant crops may be an intriguing topic to investigate for abiotic stress improvement. Novel technology breakthroughs in the previous decade have highlighted the potential of *de novo* domestication of wild plants as a realistic approach for

developing abiotic stress-tolerant crops while ensuring food safety and security. Several biotechnological strategies are being proposed to get a better knowledge of the cytokinin-related gene and various phytohormonal pathways involved in plant responses to abiotic stress. In order to generate stress-tolerant crops, new generation tools are now accessible that enable precise genome editing in specific genes. Genome editing is an excellent approach for speeding up the development of enhancing tolerance to abiotic stresses. However, there are only few studies that describe the use of CRISPR and cytokinin-related genes to enhance abiotic tolerance in commercially significant crops (Table 2) (Ogata et al., 2020; Wang et al., 2022). Clustered regularly interspaced short palindromic repeats (CRISPRs) and CRISPR associated (Cas) proteins, or CRISPR/Cas, when integrated with *de-novo* domestication becomes an ideal strategy for modifying plant genome that has a potential to be one of the most promising possibilities to enhance stress tolerance.

Future prospects

There is mounting evidence that cytokinin plays a number of roles in plant responses to various stress. Stress-related cytokinin signaling pathways and several genes that encode cytokinin metabolism enzymes have been identified as functionally significant, although little is known about their downstream components. Remarkably, the majority of the same components engaged in cytokinin regulated development are also implicated in the stress response. This suggests that there has been no distinct evolution of stress response modules, but rather the response to stress is intricately associated with the control of development. In this regard, a better understanding of cytokinins interactions with known stress response pathways would improve our understanding of the hormone's function in regulating growth-defense trade-offs. To get a better understanding of the downstream events of the cytokinin signaling pathway and to identify linkages to traditional stress response pathways, refined genetic techniques and system analysis will be critical.

Many of the cytokinin responsive genes are engaged in signaling, metabolic, and transport systems that affect plant growth and development, and next-generation technologies have revealed insights into global transcriptome alterations in connection to cytokinin responsive genes (cytokinin response factors (CRFs), *CKXs, ARR1, ARR10,* and *ARR12*) (Shi et al., 2013; Abdelrahman et al., 2021). At the transcriptome and proteome levels, genome-wide investigations may reveal interaction protein–protein networks that regulates biological development processes in growing crop plants. Global insights into molecular mechanisms and genes involved in abiotic stress tolerance are viable targets for the development of novel strategies for crop improvements. Furthermore, many studies on the influence of cytokinins on stress are conducted in controlled conditions, suggesting that cytokinins are stress modulators that function through a growth-defense trade-off (Cortleven et al., 2019). Influences of cytokinins on genotype–environment interactions are still poorly understood in natural and/or in-field agricultural settings, and future studies should focus more rigorously on testing cytokinin stress modulation in natural environments for agricultural ecosystem management, especially in the context of climate change. Understanding the functions of cytokinin, a key growth-regulating hormone in stress defense is particularly vital for understanding the influence of a changing environment on plant development and ensuring the sustainability of food supply.

Concluding remarks

The significance of cytokinins in the regulation of key developmental processes has become more apparent in recent years, providing new insights. While significant progress has been achieved, the true challenge remains in deciphering the molecular mechanisms by which cytokinins govern these developmental processes. In general, cytokinin signaling and metabolism are important for abiotic stress tolerance, and manipulating genes in the signaling pathway in major crops might be advantageous for long-term agricultural sustainability. Furthermore, the growing amount of molecular data adds to our understanding of cytokinin interplay in its developmental aspects while also adding a new degree of complexity. In addition, there are several crosstalk pathways with other plant hormones that aids to the cytokinin large pleiotropy in stress-induced growth regulation.

Furthermore, the genetic mechanism behind abiotic stress has been unravelled with the recent advancement in genomics and transcriptomics technologies. Stress tolerance genes in CWRs and other cultivated crops may be mapped using transcriptome profiling, a powerful tool. Because of recent developments in next-generation sequencing (NGS) technology, it is now possible to create high-quality pangenomes for a wide range of crops, giving researchers a full picture of genetic diversity within each species as well as the total gene pool for each specific crop. It is now feasible to implement next-generation breeding effectively for a complex trait like abiotic stress tolerance by combining *de novo* domestication with genome editing tools like CRISPR/Cas system.

Author contributions

SM, MG, and UA: conceptualization, review structure, literature survey, and writing major original draft preparation. DS, NK, TM, MR, NJ, SJ, ML, RT, MK, R, DP, AM, AG, PB, and JP: writing-reviewing and editing, tables and figures preparation,

revision, data curing, suggestions, response, and guidance. AD: conceptualization, planned and designed review structure, critically revised the manuscript, overall guidance, supervision, suggestions, and final draft. All authors contributed to the writing or revision of the final manuscript. All authors have read and approved the final version of the manuscript for submission to this journal.

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Author UA was employed by the company CytoGene Research & Development LLP.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Promising botanical-derived monoamine oxidase(MAO) inhibitors: pharmacological aspects and structure-activity studies

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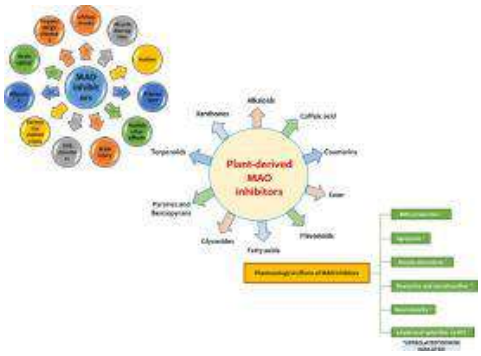
Abstract

Monoamine oxidase (MAO) is capable of catalysing the oxidative deamination of amines and neurotransmitters. MAO plays a pivotal role in maintaining neurotransmitters linked to neurological disorders *viz.* Alzheimer's disease (AD), Parkinson's disease (PD) etc. Therefore, inhibition of MAO can be implicated to the cure of such diseases. Synthetic MAO inhibitors are known to inhibit MAO activity. However, there are safety issues with synthetic MAO inhibitors and many of their effects are non-selective and irreversible. Contrasting synthetic drugs, plant-derived natural products have been popularized globally owing to their extensive acceptability and applicability, therapeutic potency and minimum side effects which potentiated the possibility of developing reversible, promising MAO inhibitors based on natural products. The present review comprehensively elucidates plant -derived natural reversible MAO inhibitors using the literature from the popular databases such as Google Scholar, Scopus, PubMed and Web of Science. This literature review reports approximately 51 plants that have been evaluated for MAO inhibitory activity. In addition, 93 plant-derived natural compounds were retrieved as MAO inhibitors. Majority of these investigations predominantly utilized an *in vitro* approach to evaluate the MAO inhibitors in relation to the developing treatments of related neurological diseases. However, *in vivo* studies and clinical trials are still lacking in evaluating the botanical-based MAO inhibitors. The aim of this review is to retrieve the recent literature to explore the *in vitro* and *in vivo* studies of plant-based natural products as MAO inhibitors, their

structure-activity relationship and relevant molecular docking analyses and their roles in the emerging therapy against disorders like AD, and PD. Further, the review also discusses the shortcomings in the existing research in order to generate more coordinated and focused research in future.

Graphical abstract



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Introduction

The enzyme monoamine oxidase (MAO, EC 1.4.3.4) was discovered by Mary L.C. Hare in 1928 in rabbit liver and was originally named tyramine oxidase (Hare,1928). MAO is located on the inner side of the outer mitochondrial membrane which contains conserved flavin adenine dinucleotide (FAD) binding domains. It contains diverse substrate-binding sites and holds membrane-binding domain (Maetal., 2004). It catalyses the oxidation of amines (primary, secondary and tertiary), amino acids and neurotransmitters (Gaweskaand Fitzpatrick,2011). The oxidation of amines via MAOs leads to the production of hydrogen peroxide (H_2O_2) and aldehydes that further cause oxidative stress leading to health problems such as neurological damage, cardiovascular diseases, obesity, and cancer (Deshwaletal., 2017; Kaludercicetal., 2014; Timisoaraetal., 2019; Vindisetal., 2000; Wuetal., 2014). MAO enzymes represent two subtypes *viz.* MAO-A and MAO-B, encoded by two distinct genes with 73% identity and are regulated by substrate specificity and sensitivity in humans (Bachetal., 1988; Maetal., 2004; Weyleretal., 1990). These subtypes vary in substrate specificity, amino acid numbers, susceptibility, and distribution in tissues. MAOs are present in various tissues like intestinal mucosa, liver, lungs, placenta, lymphocytes and brain (Kalgutkaretal., 2001). MAO-A and MAO-B are present in most mammalian tissues. Rat MAO-A is dimeric whereas human MAO-A is monomeric that oxidizes theserotonin, norepinephrine, tyramine, and dopamine neurotransmitters. Human MAO-B is a dimeric enzyme that oxidizes benzylamine, dopamine, tyramine and phenylethylamine neurotransmitters (Bindaetal., 2004; DeColibus etal., 2005; Tongetal., 2013; Wangand Edmondson,2007). The alternation of MAO levels in human tissues is associated with several neurological diseases such as Brunner syndrome, autism, schizophrenia, depression etc. (Brunneretal., 1993; Cohenetal., 2011; Tongetal., 2013; Wyattetal., 1979).

MAO inhibitors, first introduced in the 1950s, are known to guard neurons from exogenous amines in the central and peripheral nervous systems (CNS and PNS). They also restrict the movements of amine

neurotransmitters and terminate dietary amines. Inhibitors of MAO are linked to the treatment of anxiety disorders, obesity, cardiovascular diseases, cancer, depression, glaucoma, PD, and AD (Bolascoetal., 2010; Corbineauetal., 2017; Peehletal., 2008; Pletscher,1991). MAO-A inhibitors possess antidepressant activity that increases 5-hydroxytryptamine (5-HT) in the brain (Youdimetal., 2006). MAO-B levels are known to rise with age and thus are linked to age-related neurodegenerative diseases, such as AD and PD. Inhibitors of MAO-B are shown to possess curative properties against the progress of PD and AD (Drozakand Kozłowski,2006; Tzvetkovetal., 2017). MAO inhibitors are categorized into three classes such as first-generation (irreversible non-selective; isoniazid, tranylcypromine, iproclozide, and isocarboxazid), second-generation (irreversible, selective; selegiline, rasagiline, bilobalides, and mofegiline), and third-generation (reversible, selective; moclobemide, amiflamine, lazabemide, toloxatone and brofaromine) used against neurological or psychiatric diseases (Lauxetal., 1995; Tzvetkovetal., 2017). Off late a number of promising lead compounds as MAO inhibitors have been cited in the recent literature such as 3-(N-cyclicamino) chromone derivatives (Takaoetal., 2020), chromone and donepezil hybrid (6-OBn) (Wangetal., 2020), b-carbolines from *Psilocybe* "magic" mushrooms (Bleietal., 2020) etc. Earlier, MAO inhibitors have been administered as the first clinically used antidepressants. However, due to severe side effects and food-drug interactions, their use had been discontinued (Blackwelletal., 1967; Helgueraetal., 2012). Irreversible MAO inhibitors are known to cause severe adverse effects *viz.* hepatotoxicity, hypertensive crisis, haemorrhages, dizziness, nervousness, insomnia, muscle aches, sleep disturbances, weight gain, and serotonin syndrome (Amsterdamand Shults,2005; Kumaretal., 2016).

Globally, depression, anxiety, AD and PD have become a huge public health problem. Worldwide depression has been increased by 49.86% from 1990 to 2017 (Liuetal., 2020). AD is one of the major common forms of dementia syndrome, which affects around 50 million people globally and nearly every year 10 million new cases are reported (https://www.who.int/newsroom/factsheets/detail/dementia#:~:text=Worldwide%2C%20around%2050%20million%20people↗,dependency%20among%20older%20people%20worldwide). Onset of PD is age-related and around 7–10 million peopleworldwideare living with the disease (Porter,2020). The treatment of these diseases causes a huge economic and emotional taxation to the family members and the care-givers. It is estimated that, in 2020, the total cost for AD treatment is about $305 billion, and it is expected that the cost continues to increase as the age of the current population increases (Wong2020). The cost is also massive for the treatment of PD and depression (Dahodwalaetal., 2020). Hence, the demand for alternative cost-effective drugs or treatments with low side effects has been increasing. In this context, bioactive compounds from natural sources appear to be promising candidates for such treatment. Earlier, a few reviews were published on the topic such as MAO inhibitors from natural products (Carradorietal., 2014), marine natural products (Hongetal., 2020), herbal natural products (ErdoganOrhan,2016), 3D-QSAR and in-silico studies on MAO inhibitors from natural products and related derivatives (Dhimanetal., 2018). A number of *in vitro* as well as in silico analyses and molecular modelling studies have proven the efficacy of such natural products as promising MAO inhibitors (DeMonte etal., 2014; Carradorietal., 2016; Gidaroetal., 2016). The present review encompasses the role of plant-derived natural products as MAO inhibitors. After analysing all published research works, it can be assumed that plant-based natural products could become promising alternatives for the development of safe MAO inhibitory drugs. This review, further enumerates different types (flavonoids, alkaloids, caffeic acids, coumarins, fatty acids, glycosides, esters, pyrones, terpenoids and xanthones) of botanical-derived MAO inhibitors, related *in vitro* and *in vivo* studies and structure-activity relationships.

Section snippets

Methodology

The information on plant-derived natural products as MAO inhibitors was retrieved from different electronic databases such as Google Scholar, PubMed, Research Gate, ScienceDirect, Web of Science, Scopus and SpringerLink. The span of cited articles was 1987–2020. Examples of the keywords and terminologies such as “plant natural products”, “medicinal plant extract”, alkaloids, coumarins, xanthones, terpenoids, pyrones and benzopyrans, glycosides, fatty acids, ester, caffeicacid,…

In vitro studies on plant-derived MAO inhibitors

The role of metabolites isolated from the plant for the treatment of depression, AD, and PD based on their ability to inhibit MAO has been widely explored. In this review, 93 compounds isolated from different plants showed varying degrees of MAO inhibitory activity.All isolated compounds were categorised based on their diverse structural skeletons.…

In vivo studies on the plant-derived MAO inhibitors

Pre-treatment with the *G. biloba* extract, EGb 761 was found to inhibit cerebral MAO of rat. The extract was found to contain a mixture of both flavonoids and terpenoids as the major active compounds. Administration of EGb761 produced reversible inhibition of MAO activity *in vivo* (in C-57 black mice). EGb761 also enhanced dopamine (DA) metabolism thus preventing neurotoxicity (Rojasetal., 2004). In contrast, a single dose of EGb761 (100 mg/kg body wright) showed no effect on MAOs levels.…

Molecular docking studies on plant-derived MAO-inhibitors

Inhibition of MAO by the phytochemicals seems to be dependent on the presence of a phenyl or hydroxyphenyl ring. Rationalized docking studies enumerated the inhibitory properties of quercetin, myricetin, genistein, and chrysin against the isoforms of hMAO-A and hMAO-B. Quercetin and myricetin both interacted with Ala111, Ile180, Asn181, Thr336, and Phe208 amino acids of MAO-A. Additionally, quercetin was found to bind to extra amino acids Gln215, Thr336, and Tyr444 of MAO-A. 4-hydroxyphenyl…

Discussion and future perspectives

Examples of plant-derived reversible MAO inhibitors *viz.* quercetin, myricetin, mulberrofuran G, harmine, 4-hydroxy-3-methoxy-8,9-methylenedioxypterocarpan, genistein, (-)-maackiain, desmethoxyyangonin, angustine, isopsoralen, psoralen, biochanin-A, luteolin, chrysoeriol and apigenin, as antidepressants and possible anti-PD agents are mentioned in this present review. Besides competitive inhibition, the importance of dose-dependence of such inhibition has also been discussed. Natural products…

Conclusion

This review presents a comprehensive account towards the development of efficacious therapy of different privileged scaffolds, including botanical-derived natural components, as potent inhibitors of different MAOs. The current review attempted to elucidate the pharmacological profile of the different classes of natural plant products in MAO inhibition. Considering the present guidelines for MAO inhibitors as third-line or fourth-line treatment, it is too early to suggest their broader…

Declaration of Competing Interest

The authors declare that they have no conflict of interest.…

Acknowledgements

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Recommended articles

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J.D. Amsterdam *et al.*
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Food Chem. Toxicol. (2010)

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A review of monoamine oxidase (MAO) inhibitors in tobacco or tobacco smoke

2022, NeuroToxicology

> *Citation Excerpt :*
> …Rodgman and Perfetti (2013) created an alphabetical index of chemical components in tobacco and tobacco smoke. We crossmatched this index with existing literature (Das et al., 2022; Hogg, 2016; Mostert et al., 2017; Sari and Khalil, 2015; Tao et al., 2005; Tripathi et al., 2018; van der Toorn et al., 2019; Vina et al., 2012) reporting on natural compounds and their structural analogs with MAO inhibitory activity. The IC50 values and Ki values for MAO inhibition of compounds so identified are summarized in Table 2.…

Show abstract

Resveratrol-based compounds and neurodegeneration: Recent insight in multitarget therapy

2022, European Journal of Medicinal Chemistry

> *Citation Excerpt :*
> …In fact, currently, the treatment of PD involves the use of selective MAO-B inhibitors such as rasagiline and safinamide [77]. RSV has been demonstrated to inhibit the MAO-B isotype [78,79] and, moreover, RSV derivatives have been

demonstrated high MAOs inhibition [80]. trans-Viniferin (Fig. 3) is a cycled dehydrodimer of RSV isolated from Vitis vinifera, that possesses multiple biological effects [81,82]....

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Probing the MAO Enzymes with a Novel Family of Quaternary Propargylamine Derivatives ↗

2023, SSRN

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Problems of Sugarcane Farmers of River Banks in Palus Tahsil, Maharashtra

Mr. Maske Satish Ashok
Assistant Professor
Dr. Khade Ashok Shrirang
Associate Professor & Head of Dept.
Ms. Madavi Asha Budharam
Dr. Patangrao Kadam Mahavidyalaya,
Ramanandnagar (Burli)

Introductions: Mainly since the establishment of Maharashtra, Sangli district is known as the leading district in sugarcane production. A large amount of sugarcane has been produced from alluvial soils along the banks of rivers in Sangli district. Co-operative sugar factories located in Sangli district depend on this sugarcane producer. Sugarcane growers are the primary source of raw material to the sugar factory. This is the second pillar of the sugar industry. The prosperity of the sugar industry depends on the regular and continuous supply of sugarcane during the harvest season. Although the farmers have a stake in the factory, they have many options to supply sugarcane for the mill. A farmer is always aware of the production and income of the farm, because they have invested heavily in sugarcane cultivation. The factory should maintain good relations with the farmers to achieve the highest target of sugar production. Sugarcane growers have some problems with sugar mills. This study focuses on the life and work of sugarcane farmers. He expects that first priority should be given to farmers. The factory should implement a welfare approach for the development of farmers.

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UPI and its Role in Eradicating Poverty from Rural India

Patil B.D., Mugali A.P.
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Introduction : Poverty eradication is a crucial goal for any nation, and in the context of India, addressing rural poverty is of utmost importance. The Unified Payments Interface (UPI) has emerged as a transformative digital payment system that has played a significant role in eliminating poverty from rural areas. This article explores the impact of UPI in empowering rural communities, facilitating financial inclusion, and driving socioeconomic development.

Review of Literature :

Research Articles:

1. Kumar V., (2021). " Adoption Of Digital Payment System In Rural Area: A Study At Ramanagara District" New Horizons XVIII, 308-310; In this research article, Kumar V. explore the role of UPI in enhancing financial inclusion in rural India through a case study on Ramanagara District. They examine the adoption of UPI in rural areas and its impact on expanding access to financial services and promoting inclusive growth.

2. Ravi, C.S. (2017). "Digital payments system and rural India: A review of transaction to cashless economy". International Journal of Commerce and Management Research, 3(5), 169–173; Ravi, C.S. investigate the specific role of UPI in enhancing financial inclusion and cashless economy in rural India. They analyze the factors influencing the adoption and usage of UPI among rural populations and explore its implications for inclusive economic development.

3. Rangaswamy, N., & Arora, P. (2016). "The mobile internet in the wild and every day: Digital leisure in the slums of urban India". International Journal of Cultural Studies, 19(6), 611–626; Rangaswamy, N., & Arora, P. present a case study that highlights how UPI has facilitated entrepreneurship in urban slum population in India. They examine how UPI-enabled digital payments have empowered slums of urban India, facilitated market access, and contributed to income generation and poverty reduction.

4. Ali S., & Akhtar W., (2017) "Digital Payments For Rural India - Challenges And Opportunities", International Journal of Management and Applied Science, Volume-3,35-40; Ali S., & Akhtar W.,conduct an analysis of UPI adoption in rural India, with a specific focus on its impact on financial inclusion & challenges as

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Global Economic Trends and India's Trade Resilience : A Post-2014 Evaluation

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Introduction : The post-2014 period in India marked a crucial juncture in its economic history, characterized by a series of ambitious reforms and policy shifts aimed at revitalizing the nation's economy and enhancing its global competitiveness. These transformative changes, including the "Make in India" campaign, the implementation of the Goods and Services Tax (GST), and efforts to improve the ease of doing business, were intended to unlock India's immense economic potential and align it with contemporary global economic trends.

As India navigated this evolving economic landscape, it became imperative to evaluate the resilience of its trade sector in the face of various global challenges and opportunities. This research paper embarks on an intricate journey to comprehend how India's international trade dynamics evolved post-2014 within the context of ever-changing global economic trends. We aim to explore the multifaceted aspects of India's trade resilience, analyzing not only its ability to withstand external shocks but also its capacity to seize emerging opportunities.

Global economic trends have been dynamic and sometimes unpredictable, encompassing the rise of protectionism, the growth of digital commerce, shifts in global supply chains, and the disruptive effects of the COVID-19 pandemic. Understanding how India responded and adapted to these trends is pivotal for policymakers, businesses, and researchers alike. This study aspires to provide a comprehensive assessment by examining shifts in trading partners, export-import patterns, trade policy reforms, and the role of India in the global economic landscape.

By investigating these intricate dynamics, we intend to contribute valuable insights that can inform future policy formulation and strategic decision-making in both the public and private sectors. Moreover, this research aims to uncover critical factors that have enabled India to maintain its trade resilience and identify areas where further improvements are needed to maximize its potential on the global stage. In doing so, we hope to illuminate the path forward for India's trade in an increasingly interconnected and dynamic world economy.

Literature Review :

1. Working paper of Embassy of India Washington (2017)"Brief on India-U.S. Relations", Ministry of external affairs [https://www.mea.gov.in/Portal/ForeignRelation/India_US_brief.pdf]

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Catalytic activity of an acidic ionic liquid as a solvent for the synthesis of Coumarin derivatives

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Introduction : Coumarin are an important class of benzopyrones being the core unit of different natural products and exhibit a spectrum of biological activity'. Naturally occurring Coumarin are found in many plants, notably in high concentration in Tonka bean, woodruff, lavender, licorice, strawberries, apricots, cherries, cinnamon, sweet clover and bison grass having vanilla like flavor, Coumarin be bound their class name to 'coumarou' the vernacular name of the Tonka bean (Dipteryx odorata willd, Fabaceae), from which Coumarin itself was isolated in 1820 by Vogel[2]. Due to the potential application in fragrance, pharmaceutical and agrochemical industries it occupies an important position in natural and synthetic organic chemistry. Coumarin comprises a vast array of biologically active compounds with several types of pharmaceutical agents possessing anticancer, anti-HIV, anticoagulant, spasmolytic and antibacterial activity, and cytotoxic activity in vitro and in vivo". Natural Coumarin, such as calanolides, isolated from Calophyllum genus has shown potent anti-HIV activity. Wedelolactone 1(Figl) is another naturally occurring product that is used as a venomous snake-bite antidote; and Novobiocin 2 (Fig 1) is an antibiotic, which acts as a competitive inhibitor of the bacterial ATP binding gyrase B subunit. Many synthetic compounds, which contain the Coumarin moiety, are well known for their odor, stability to alkali, and availability. They are widely used in perfume, soaps and detergents and in the preparations of insecticides, optical brightening agents". Coumarin was once used as a food flavoring, but was banned by the FDA due to carcinogenicity. Some 3-substituted and 7-hydroxycoumarins have been shown to act as photo table laser dyes that emit in the blue-green region of the visible spectrum. The emission range increases when the 3-substituent is a heterocyclic moiety9, Coumarin also act as intermediates for the synthesis of furocoumarins, chromenes, coumarone and 2- acylresorcinols.

Because of their varied biological activities, the preparation of Coumarin and its derivatives has attracted the attention of organic chemists. Various synthetic methods have been developed for the synthesis of Coumarin. These include use of the Knoevenagel condensation, Wittig reactions, Perkin reaction and Pechmann reaction.

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Nanoparticle Synthesis Methods : Bridging Innovation and Precision

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Mr. Prashant Kundalik Bhagyawant (Asst. Prof.)
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Introduction: Nanoparticles are tiny particles with dimensions in the nanometer range, typically between 1 and 100 nanometers. They can be composed of various material, including metals, semiconductors, polymers, and organic or inorganic compounds.[1] The unique properties of nanoparticles arise from their small size, which leads to a high surface area-to-volume ratio and quantum effects.[2]

Key Characteristics of Nanoparticles:

1. Size: Nanoparticles are extremely small, often on the scale of atoms and molecules, ranging from 1 to 100 nanometers.

2. Surface Area: Due to their small size, nanoparticles have a high surface area relative to their volume, which makes them highly reactive and useful for various applications.

3. Quantum Effects: At the nanoscale, materials exhibit quantum effects that differ from the properties observed in bulk materials. These effects can include changes in optical, electronic, and magnetic properties.

4. Versatility: Nanoparticles can be engineered to have specific properties by manipulating their size, shape, and composition. This versatility makes them valuable in a wide range of applications.

5. Interactions: Nanoparticles can interact with biological systems, tissues, and cells in ways that larger particles or bulk materials cannot. This property is exploited in various fields, including medicine and biotechnology.[3]

Objectives:

• Provide an overview of major nanoparticle synthesis methods.

• Explore recent advancements in nanoparticle synthesis techniques.

• Discuss the potential applications of nanoparticles synthesized through different methods.

Challenges and Concerns:

1. Toxicity: The potential health and environmental impact of nanoparticles is a concern, especially when they are used in consumer products or medical applications.

2. Regulation: Due to the unique properties of nanoparticles, regulatory frameworks may need to be adapted to address their specific challenges and ensure safety.

3. Ethical Considerations: The ethical implications of using nanoparticles

A New National Research Foundation : A tool of Intellectual and Material Wealth

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Introduction : The national educational policy 2020 is the first education policy of the 21st century and aims to address the many growing developmental imperatives of our country. This policy proposes the revision and revamping of all aspects of the education structure, including its regulation and governance, to create a new system that is aligned with the aspirational goals of 21st century education, including SDG4, while building upon India's traditions and value systems. The National Education Policy lays particular emphasis on the development of the creative potential of each individual. It is based on the principle that education must develop not only cognitive capacities- both the 'foundational capacities' of literacy and numeracy and 'higher-order' cognitive capacities such as critical thinking and problem solving- but also the social, ethical and emotional capacities and dispositions.

The purpose of the education system is to develop good human beings capable of rational thought and action, possessing compassion and empathy, courage and resilience, scientific temper and creative imagination, with sound ethical moorings and values. It aims at producing engaged, productive and contributing citizens for building an equitable, inclusive and plural society as envisaged by our constitution. A good education institution is one in which every student feels welcomed and career for, where a safe and stimulating learning environment exists, a wide range of learning experiences are offered, good physical infrastructure and appropriate resources conductive to learning are available to all students. Attaining these qualities must also be seamless integration and coordination across institutions and all the stages of education.

The fundamental principles that will guide both the education system at large, as well as the individual institutions within are: recognising, identifying and fostering the unique capabilities of each student, by sensitizing teachers as well as parents to promote each student's holistic development in both academic and non- academic spheres. According to highest priority to achieving foundational literacy and numeracy by all students by grade 3. Learners have the flexibility to choose their programmes, their own paths in life according to their talents and interests. There is no hard separations between arts and sciences, between curricular

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Racial Discrimination in Dennis Brutus's Poem Letters to Martha

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The present paper focuses on Racial Discrimination in Dennis Brutus's Poem Letters to Martha. Dennis Brutus is a South African poet. His poetry is the proof of the fact that the artist in him has always functioned in African society and as the voice of vision in his own times. Dennis Brutus was in exile. He was arrested, imprisoned and shot while trying to escape from South African police. He had an active political life. He was the president of the South African Non-Racial Olympic committee. He wrote about what he had seen around him. He wrote about racial discrimination, apartheid regime and white supremacy in South Africa. He fought for freedom, justice and peace in South Africa. His poetry is a direct response to a horrible socio-political situation. Every page of his poetry bristles with images of searing pain, spilling blood, contorting hearts or wracking nerves, His poetry shocks, stimulates, agitates, educates and activates us about the South African society and South African reality. His voice is the voice of the people. His poetry is a socio-political discourse of the South African situation.

Dennis Brutus's A **Simple Lust** was first published by Heineman Educational Books in 1973. It's Part I contains Sirens, Knuekles, Books and Other Early Poems. And part II consists of **Letters to Martha.** This second section includes early poems, poems about prison, poems written while arrest and into exileDennis Brutus fights with fear of the coloured South Africans about the whites in his poetry. His understanding of 'the anonymous powers of fear and its corrosive action makes it easier for him to forgive treacherous and indifferent South African blacks. In **Letters to Martha,** there are eighteen letters along with **Early Poems, '**Poems about prison' and 'Postscripts'. The first letter is about the fear of the inmates in prison. Even in prison the inmates are full of apprehensions that arise from

The load of approaching days
Apprehension-
The hints of brutality

After the sentence, there is a feeling of fear and the prisons are appalled to see the nails and screws of steel. They are filled with 'the steel-bright horror' to see the knives in the morning air.

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Problems of Sugarcane Farmers of River Banks in Palus Tahsil, Maharashtra

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Introductions: Mainly since the establishment of Maharashtra, Sangli district is known as the leading district in sugarcane production. A large amount of sugarcane has been produced from alluvial soils along the banks of rivers in Sangli district. Co-operative sugar factories located in Sangli district depend on this sugarcane producer. Sugarcane growers are the primary source of raw material to the sugar factory. This is the second pillar of the sugar industry. The prosperity of the sugar industry depends on the regular and continuous supply of sugarcane during the harvest season. Although the farmers have a stake in the factory, they have many options to supply sugarcane for the mill. A farmer is always aware of the production and income of the farm, because they have invested heavily in sugarcane cultivation. The factory should maintain good relations with the farmers to achieve the highest target of sugar production. Sugarcane growers have some problems with sugar mills. This study focuses on the life and work of sugarcane farmers. He expects that first priority should be given to farmers. The factory should implement a welfare approach for the development of farmers.

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Water Examination and Analysis Process

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Introduction : The most valuable natural resource for our daily life is water. Even while water makes up almost the entire land surface, only a small percentage of it is actually available, making it an essential resource. Water resource are limited, so, must be used with carefully. Water must be careful before use. Polluted water and water bodies is not good indicator for environmental degradation, it is also a dangers for the human being and ecosystem also. There for Water sources checked for the regular uses it's for good to human life or industries also. Good Water quality always better for human being and environment also. Water quality related to the content of physical, chemical and biological in water. Polluted water and water bodies is harmful to the ecology as well as being a sign of environmental degradation. In the industries there were water quality are very hard or poor so that is very bad significant to financial loss. So Examine or Analysis of the water's quality is necessary before using. We use water for a various purpose; hence we must be careful to when using it. Water can be used for drinking, everyday tasks of our life, industry, agriculture, and other purposes. In other word chemical, physical, and biological standards are required for each use in order to achieve the objective that was set. Standards for water quality are implemented to guarantee that water is used appropriately and efficiently for intended purposes. The purpose of a water quality analysis is to measure the necessary. Water parameters are using for the accepted practices and determine if the results meet standards. The primary function of water quality analysis is monitoring. Among the significance of this evaluation are followings:

· To determine if the water quality satisfies the requirements and is thus appropriate for the intended application.

· To monitor the water quality and efficiency of the system.

· To keep an eye on whether the requirements for water quality can be achieved. Analysis of water quality is important for the public health and industrial use.

Water Quality Analysis Procedures :

The processes for an analysis of the general water quality is following.

1. Collect the Water Sample
2. Selection of Methods

Historical Perspectives of Tribes reflected in Louise Erdrich's 'Tracks'

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Introduction: The novel Tracks argue that the space between the Native and Western world's demands re-conception of home. It also suggests a type of warning to Natives who lose their connections to land, family, culture, language i.e. home. Home is not just a restoration but its power should not be transgressed, or the price of it may be too dear. Louise Erdrich's novel emphasizes the undeniable link between culture, place, heritage, people, imagination and time. Evers continues, 'By imagining who and what they are in relation to particular landscapes, cultures and individual members of cultures form a close relation with those landscapes.

The present novel relates the consequences of Fleur Pillager's selfish quest for revenge on the man named John James Mauser who stole her land. In order to enter Mauser's residence to kill him, Fleur changes her appearance as a maid in need of work. She is successful in this initial task. Her desire to make Mauser suffer all the more, ironically, ends with her accepting Mauser's an emotional request for life. She offers to take her as his new wife. Her decisions are distinct disadvantages to her, her family, and community. Fleur's temporary stay leaves her an alcoholic, daughterless, and the mother of Mauser's mixed-blood, mentally deficient son. Only in coming home does Fleur survive the ordeal, some pieces of her life never return.

In Tracks, Natives negotiate the conflicting forces of Native and Western ideologies to ensure their cultural, social, and economic survival. Tracks portray home theme in its most traditionally Native sense. The plot centres on the seemingly hopeless fight to keep Pillager and Kashpaw homelands. This struggle is worsened by in-clan fighting and the eventual split of mixed-blood families as Morrissey and Lazarus who wish to sell their lands.

John Gamber have done much to argue similar points, it is also beneficial to view Erdrich's Tracks in light of Edward Said's understanding of Poetics of Space. Said contends 'The objective space of a house its corners, corridors, cellar, rooms are far less important than what poetically it is endowed with, which is usually a quality with an imaginative or figurative value we can name and feel'. Erdrich's Tracks is the creation of the world and its people with such fidelity and power that they become part of the common memory. Place, Imagination, people,

The Transformative Power of Artificial Intelligence in E-Commerce

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Introduction : AI is driving personalization and recommendation systems, enabling e-commerce platforms to deliver tailored shopping experiences. Machine learning algorithms analyze vast amounts of data, considering user behavior, preferences, and browsing history to offer product recommendations that enhance customer satisfaction and boost sales. This customization not only increases conversion rates but also fosters customer loyalty. Furthermore, AI-powered chatbots and virtual assistants are improving customer service, providing immediate responses to inquiries, resolving issues, and even assisting with purchase decisions. These conversational AI agents are available 24/7, delivering a more efficient and engaging shopping experience. Supply chain management is another area where AI is making a profound impact. Predictive analytics and AI-driven demand forecasting optimize inventory levels, reduce warehousing costs, and minimize stock outs. Additionally, AI enhances logistics and delivery through route optimization, real-time tracking, and last-mile delivery solutions, leading to faster and more cost-effective shipping. AI's data analytics capabilities are revolutionizing marketing strategies. It enables businesses to segment their target audience, develop hyper-personalized marketing campaigns, and analyze customer sentiment through sentiment analysis. AI-driven marketing automation tools also streamline marketing efforts, allowing e-commerce platforms to reach their audience at the right time with the right content.

1. Meaning of E-Commerce : E-commerce, an abbreviation for electronic commerce, enables the exchange of goods and services over the internet. It's akin to operating a virtual store where individuals can peruse items, make transactions, and finalize purchases without the necessity of visiting a brick-and-mortar location. E-commerce has revolutionized the way people shop and conduct business, providing the convenience of online shopping and transactions around the clock, all from the convenience of their homes.

1.2 Meaning of Artificial Intelligence : Artificial Intelligence, commonly known as AI, is a branch of computer science dedicated to designing intelligent systems that mimic human-like thinking. This involves the creation of software

IMPACT OF WORK FROM HOME ON EMPLOYEES PSYSCHOLOGY AND WORKSATISFACTION - A STUDY

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Abstract

The paper discusses on Impact of Work from home on employees psychology and work satisfaction – a study. Work from home is described as individuals receiving remuneration from their employer for working from their home or from other location of their choice. The COVID-19 had gradually changed the way people live and work and it is one of the biggest changes the world has ever witnessed. It had posed major risks to employees, exposure to the virus and income loss as well as dramatic loss of human life worldwide and presented an unprecedented challenge to the world of work, public health and food systems. The COVID-19 pandemic and the affected lockdowns have made work from home an imperative for several companies, institutions and industries. After the declaration of lockdown more than 3 billion people, excluding the essential workers like defense and healthcare officials, had been pushed to work from home. Most of the corporates had no other option than providing flexible working conditions including work from home. Work from home is a lot more comfortable thing for the many of employees. And also employees can save much of the time and money as they do not have to travel so far which means employees have more time to work and even for themselves too. Job security is a major stress factor during the COVID-19 pandemic, which decreases job satisfaction and raised concerns about mental health.

Keywords: work from home, COVID-19, pandemic, work satisfaction, stress, job satisfaction

Introduction

Work from home is described as individuals receiving remuneration from their employer for working from their home or from other location of their choice. COVID-19 was a new disease that had begun circulating worldwide in the human people since December 2019. The director General of the World Health Organization declared the novel Corona virus disease 2019 (COVID-19) as a pandemic on 11th March, 2020, it was marked the beginning of a major interruption of normal working life for people around the world. The virus of COVID-19 had begun to spread worldwide. And the result was that some of the Governments had imposed and re-imposed strict lockdowns throughout the country. The COVID-19 had gradually changed the way people live and work and it is one of the biggest changes the world has ever witnessed. The pandemic situation of COVID-19 had moved to a spectacular loss of human life worldwide and presented an unprecedented challenge to public health, food systems and the world of work. Most of the enterprises and companies had faced an existential threat. During lockdowns without the means to earn an income, many were unable to feed themselves and their families. The COVID-19 pandemic had altered

every aspect of human being from food, shelter, education to work life. In response to overcome the pandemic situation the organizations, corporate companies, IT companies and institutions stimulated their employees to work from home full time remotely to stay safe. To work from home one should need to make sure having technology, internet service, and workable schedule can stick to and ways to connect with others. The concept of Work from home redefined as conventional that was typical only for certain types of work, on an occasional basis, or given unique employee circumstances. Work from home benefited to employers as it boost productivity, reduce turnover, and lower organizational costs, while on the employees point of view they enjoy perks like flexibility and the lack of a commute. For many employees, working from home is the holy grail of employment options. Most of the employers and employees are expecting to implement permanently more flexible work from home opportunities after pandemic. People choose to work from home for various reasons such as to spend less time in the office, more time with the family members.

1. Objectives of Study:

1. To assess the different problems faced by the employees at the time of work from home.
2. To understand impacts of work from home on employees psychology.
2. To understand impacts of work from home on employees work satisfaction.
3. To offer suitable suggestions.

3. Research Methodology:

The present research study is based on secondary tools. The analysis method has been adopted by collecting information from reference books, newspapers, online data etc. for which the definite meaning of the concept can be explained by the analysis.

4. Impact of Work from home on Employees Psychology and Work Satisfaction

Work from home also known as remote work, mobile work, teleworking, telecommuting, homework, outwork and the flexible workplace, it means a work arrangement in which employees need not commute to their workplace or office in the company. It had been seen over the last two years at the corporate work culture that a major overhaul as the corona virus pandemic affect the world in 2020. Majority of the companies, institutions, and organizations decided to remote work and work from home concept. Some of the benefits can be cited from the working from home which includes familiarity and comfort, flexibility, undisturbed working, no travel, self-management, being with the children etc. The employees increased fear over uncertainty of their employment and stability of the future income which leads to stress and depression. As Herzberg says, performance outcomes is a source of both job satisfaction and dissatisfaction which occur because of certain workplace circumstances and hygiene factors. Job security is a major stress factor during the COVID-19 pandemic, which decreases job satisfaction and raised concerns about mental health. COVID-19 has changed the way of life and work and had led to rising mental health problems, stress and anxiety among employees. Due to work from home, employees need to be available for video calls even outside of their scheduled working hours or face having to complete

household tasks while at work. This may hamper the boundaries which employees set for their own work-life balance. In severe circumstances employees experienced depression, which marked low mood, exhaustion, pessimism, poor sleep, feeling helplessness and hopelessness. Some of the factors affected due to work from home on employees psychology are that feeling exhausted, lethargic, and have had trouble sleeping, depression, panic attacks etc. Even work performance also declined over this period of pandemic. As well as the obstacle of work from home is that too many work demands from the employers on time may increase the stress levels of employees. And even other psychosocial effect on working employees which includes frequently reported increased anxiety, disorientation, anxiety and a sense of urgency (World Health Organization, 2005). Besides this it had found that the job satisfaction of employees increased by remote work, including income, working hours, free time, appropriate physical activity. Work from home and job satisfaction are positively correlated. Along with working from home impacts on work satisfaction as employees are their own bosses, flexible working hours, do not have to deal with unpleasant colleagues, reduced stress, saving time, closer to their private life, spend more time with family, increasing productivity, less work exhaustion etc. (Baruch 2000, Bellmann/Widuckel 2017, Gregory 2016, Grunau et al. 2019, Johnson 2015, Shamir/Salomon 1985). As well as a better work-life balance is mentioned quite often as the most important benefit of work from home. Having a better work-life balance is frequently cited as the top perk of working from home.

5. Conclusion and Suggestions:

One could call the COVID-19 crisis a "game changer." Working from home or remote work is a fantastic alternate work arrangement that organizations introduced during the COVID-19 pandemic situation in many countries. In the beginning, working from home itself contributes to higher satisfaction. This effect, nevertheless, is not enduring. Working from home impacts on psychology of employees. Adopting working from home can contribute increased workload. There may a temptation to work longer hours, and for those who do not have a home office, there may no distinction home and office life. Even the video meetings can trigger fatigue to employees. These all things may adversely effects on psychology of employees like stress, anxiety, fear of discontinue of job. For overcoming from stress, anxiety due to work from home employees should adopt self-care strategies because it is good for their mental and physical health and can help to work smoothly. For improving mental health of employees the employers should be schedule smaller scale meetings which can also improve the mental health, by giving participants more space to engage with their team and having their contributions personally acknowledged. Employees should be mindful about their physical and psychological health from their daily routine life. Such as to get enough sleep, participation in regular physical activity, eat healthy, avoid tobacco, alcohol and drugs, limit screen time, relax and recharge, focus on positive thoughts, connect with others. "The brain is like any other muscle. It needs to rest," says Kramer. "Go for a walk, get some exercise, stretch. Then get back to work."

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Theoretical Introduction of Photocatalysis and its Application : A Review

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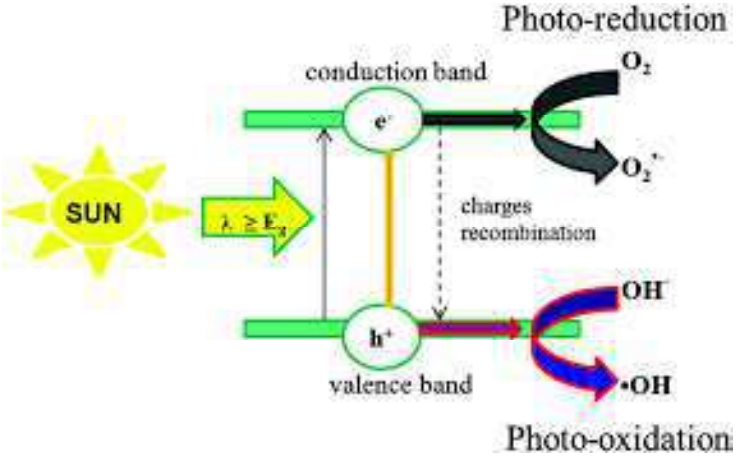
Introduction : When a light source interacts with a material's surface (i.e. semiconductor materials) the process or activity known as "photocatalysis. For this process, at least two processes must occur at the same time; an oxidation reaction using photogenerated holes and a reduction reaction using photogenerated electrons. The photocatalyst species itself should not alter in any way while the process is underway, hence the two aforementioned processes must precisely synchronize at the same time. Earle 1972, Fujishima and Honda are recognized as the pioneering scientists who successfully accomplished electrochemical photocatalysis of water at a semiconductor electrode.[1] Subsequent research revealed that TiO_2 (titanium dioxide) aids in the breakdown of cyanide in water, which in turn led to an increase in interest in the material's potential environmental uses.



Fig,1- Basic reaction mechanism of photocatalysis

The decomposition of various pollutants and improvement of atmospheric quality are both possible in a real-world setting through the effective and practical application of photocatalysis. As a result, the building and construction sector can employ the photocatalysis process to enhance indoor air quality. With the aid of doped or undoped nanostructure materials, possible photocatalytical applications

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Use of D-Technology in Teaching of Literature

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Abstract:

In modern English, digital technology represents a significant advancement. Technology helps students learn more effectively and enables teachers to improve their instruction and whole process of teaching and learning. Modern English teachers fully embrace a number of educational promotion strategies. The present paper presents how literature and culture combined with technology can be used to improve student learning effectively.

Keywords: Multimedia, ICT, technology, literature, e-book, computer, book, Internet, web, etc.

Introduction:

Technology is an integral part of students' life, which is why they seek to find it in the teaching process as well. As a result, the academic staff has begun to develop educational programs that offer a variety of didactics. Community activities, group projects, online platforms and other teaching strategies motivate students to study in ways similar to their individual preferences. In this scenario, the introduction of technology into learning programs is no longer a choice but a necessity, a very important tool for both students and academic staff. The generation of digital born uses the technology, by transforming different occasions, sounds and images from one territory to another, from one screen to another, in notebooks, smartphones, iPods, iPads, etc. This generation has a different perception of time. It is 'multitasking', which means that they can accomplish many things at the same time, such as: studying, sending messages, chatting with others; everything at the same time and in a very astonishing way. Innovative processes, nowadays, are becoming everyday more and more main components of the educational system as students, being most of them part of the 'digital migrants', are urging their lecturers to be included in their world, which changes very quickly and continuously. Education starts from communication. The current generation of students is always asking lecturers to undertake new roles. They are asked to introduce the new materials in a new format, more communicative and direct, through which they can be accessible and exchanged mutually.

In the field of literature these challenges reinforce the perspective that literature is at the same time a place of communication and an expression of artistic expression created through the science of linguistics. By communicating, the lecturers convey knowledge and achieve feedback from the students, and then this enriched knowledge is brought back to them by creating complete exchange cycles. Constantly, conversations extend beyond classes through forums in all types of media.

The Impact of digital technology in literature:

The technology and tools provided by it provide a unique platform for both the well-known authors and ordinary people. People today freely express their thoughts using electronic media such as blogs and social networks. Technology today also enables one-to-one correspondence between an author and a reader, simplifying access to and understanding of literature by students, researchers, and readers. Online literature access by academics is increasing day by day. An increasing number of academic institutions are designing their online courses such as courses in literature, linguistics, creative writing, etc. Among the key events that characterize the rapid development of technology, there is the development of multimedia, a technology that brought together hardware and software. It was called digital fusion: the melting of digital technologies based on computer usage. The development of multimedia, featuring Hypertext and E-books, brought radical changes in the field of literature because they revolutionized the way of writing and reading.

Contribution of Technology in the study of literature:

By using technology, students acquire a higher level of control on sharing knowledge: they can access information, learning fields, as well as other sources in the most appropriate time for them and according to their engagements and lifestyle. Technology helps them to choose the time of accessing information sources, which can be integrated within the study course and can be completed after the auditoriums, in libraries or with standard methods of knowledge distribution.Even if they are not physically (or temporarily) together, they can communicate and discuss their ideas with each other. Technologies such as emails or other communication platforms provide them with precious environments in which communication can continue even outside university auditoriums. The study of literature through multimedia represents a new technique, which is more attractive compared to traditional books where verbal comprehension is predominant. It creates interactive

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activities and provides students with opportunities to study authors and textbooks using a variety of media and sources of information. It involves collaborative work and turns out to be a powerful catalyst for cooperative learning. Students use a wide range of strategies to experience, understand, interpret, and evaluate the texts.Students and their lecturers share sources of information by encouraging a way of interdisciplinary thinking as well as a cross-curricular approach. The style of studying is best suited to teaching methods and thus becomes more effective and more efficient. The variety of materials and integrated methods motivates students more. They manage to create their ideas in a new format, using visual language, in addition to spoken and written language. The use of multimedia supports constructive learning - students build thinking patterns to understand the world around them, or else they manage to build knowledge structures. Moreover, multimedia supports learning independently through information and events control. However, today we can use a list of more developed applications to help students and lecturers.These applications do not only offer students free of charge a significant number of texts in differentformats, but also provide information on how to understand these textbooks by developing their desire for reading and literature. I am mentioning some of these applications:

Goodreads – Designed to help find and use shared books. Students can exchange recommendations for different books or suggest new books based on the preferences they have expressed in online communities. In addition, they can categorize and make reviews of favourite books, or keep book entries in reading. This app contains over 2000 eBooks.

Audible – It is quite valuable, especially for those students who have difficulty concentrating. Through the application, users can hear hundreds of thousands of audio books, enabling labeling of different parts while reading. This application, giving students the opportunity to earn different badges, motivates them to read / listen.

SparkNotes – through this application, students can read book reviews, character reviews, and general analysis of literary works. If a copy of a current book is not available, the application helps students in the best sense of a reading or finding information to include in their literary theses.

Literary Analysis Guide – an application to assist in the preparation of literary analysis theses or any other related activity. It is equipped with three mechanisms that contain information about poetry, prose, and rhetoric. Using these mechanisms, students can access summaries and examples of more general literary terms that help them further in performing their literary assignment.

Literary Review – professors who are increasingly looking for the latest developments in the world of literature can use this application. Although full access requires subscription in the Literary Review, the cost is personal, nominative and gives access to the latest publications in many genres and critical literary discussions. The application also provides the ability to search previous publications to find teaching-related articles.

Kindle – an app that gives users the ability to download eBooks from Amazon directly to a smartphone or tablet. To read eBooks the app is also equipped with a vocabulary and offers the ability to read and transfer to PDF format.

Conclusion:

Today we can say with conviction that the time of literary teaching based solely on literary text is ending. It is true that the teaching of literature in today's world, dominated by technology and multimedia, is becoming more and more complicated. But at the same time information and communication technology sources can be the solution to the challenges faced by professors in order to incorporate and motivate their students in literary studies. Technology provides ways to find the best research methods and techniques, the method for disseminating study material, provides advanced search tools, and can also provide the page that helps the teacher guide the student in implementing new techniques. It helps to studying and experimenting; a new teaching method adds an interest to the subject. But we should bear in mind that technology is only one approach that needs to be adopted, the success of this method is not guaranteed at all costs, but with a well thought-out use and appropriate integration in the subject matter, it can become an extremely effective tool important for both the lecturer and the student.

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Understanding Humanities in William Dalrymple's In Xanadu : A Quest

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Introduction : One of the essential aspects of human existence is travel. Travelling is a trip, whether it is across town or to a distant country, and it alters history, the person telling the stories, and themselves**.**

According to its etymology, the word 'travel' comes from the verb 'travailen,' which means 'to make a journey.' Its original meaning was 'to toil, labour.' Therefore, the idea of 'go on a difficult journey' may have contributed to the semantic evolution. In the richness of the English language, there are even phrases that signify "travel," such as 'movement,' 'mobility,' 'tour,' 'errand,' 'wandering,' 'trip,' and so on. Almost every one of these words refers to moving from one location to another.

In Xanadu: A Quest, William Dalrymple makes his literary career as a travel writer who is expected to become a bright star. Published in 1989, the book embodies all the characteristics of travel writing, with Dalrymple's clever adoption of Marco Polo's route—from Jerusalem to Shang tu in China, known in the West as 'Xanadu,' a term Samuel Taylor Coleridge used to refer to the region—following Marco Polo's footsteps from the Middle East into China.

In addition to being a bestseller and winning the Yorkshire Post Best First Work Award and Scottish Arts Council Spring Book Award in 1990, the book gained enormous popularity. After learning about the proposed opening of the Karakoram Highway in eastern Asia during his final year of study, William decides to follow the entire Marco Polo route, which he initially claims to be the first of its kind. He says, "It was my then girlfriend Louisa who spotted the small article in the New York Herald Tribune which announced the opening of the [Karakoram] highway and together we decided to mount an expedition to follow in the Venetian's footsteps."

Many had, like us, set off in his tracks but no one had ever managed to complete the journey. … But in the spring of 1986 the opening of the Karakoram Highway, the mountain road which links Pakistan with China, made it possible for the first time, perhaps since the thirteenth century, to plan an overland route between Jerusalem and Xanadu and to attempt to carry a phial of Holy Oil from one to the other. The war in Afghanistan prevented the whole of Polo's journey

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Feminist Posthumanism in Manjula Pdmanabhan's Dystopian Novel *Escape*

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Abstract

In the 21th century, every aspect of human life has been reshaped by technology. Man's curiosity about life and unquenched thirst for power causes unending cycle of progress and has made us what we are. It gives rise to life full of complexities and unresolved knots. People are entangled in co-constitutive relationships with nature and the environment with other animals and organism with medicine, technology, and science. It creates many questions before humanity. Humanity means the things that make us human. The writers have the power to heal and guide the society with their words and insights. Even writers can offer a sense of solace and expose the needs that make world better. They have power to change the culture. Writers through their writing also explore their view about humanity and post-humanity. The present paper tries to explore the feminist posthumanism in Manjula Padmanabhan's dystopian novel *Escape.*

Keywords: Posthumanism, dystopian, utopia,feminism , patriarchy

Because of this during the last years, there is a sudden increase in the popularity of a particular genre within Science Fiction that is dystopia. Nowadays the dystopian genre is almost familiar to every one of us. There are also some movies that based on literary dystopia which attract the attention of researchers. The most common feature of dystopian is the lack or degradation of moral values. The present research work focuses on feminist post-humanism in Manjula Padmanabhan's dystopian novel *Escape*. The analysis has focused on some specific dystopian features like image of post-human women, journey of female characters from non-human to post-human, the hierarchy and gender roles in novel. A feminist is someone who supports equal right for women means a person who believes in and supports feminism. The word feminist comes from feminism, which originally meant simply "being feminine", or "being women". If person believe that women should have the same political, social and economic rights as men, then that person is feminist. Feminist theory is the extension of feminism into theoretical, fictional or philosophical discourse. It examines women's and men's social roles, experiences, interests, chores and feminist politics in variety of fields such as sociology, home economics, literature, education, philosophy and other. In literature feminist theory often focuses on analyzing gender inequality. It generally explored the themes like discrimination, oppression, sexual objectification, patriarchy and comodification of women. The present paper tries to explore the dystopian society in which gender inequalities are intensified.

There is combination of three terms in post humanism. First is human, which marked by his thinking / intelligence, who is able to plot his / her own course of action on needs, desires, wishes. Second term is humanism which means the study of individual subject and composite features. It treats the human subject as at the centre of the human's thoughts and actions. It is a rational philosophy informed by science, inspired by art, and motivated by compassion. It gives emphasis on the principle that human beings have the right and responsibility to give meaning and shape to their own lives. It emphasizes a concern for humans in relation to the world.Post humanism is a recent trend in literature which means "after humanism" or beyond humanism. It refers to technologically engendered nonhumans or post humans. Post humans are smarter than humans like aliens. Common human beings can't understand them. Post humanism explores the nature of the human in the age of advanced biotechnology, genetic engineering, and computers. Posthumanism refers more advanced human. Sci-fi dystopian novels describe the future course of human evolution. Posthimanism tries to explain the new conceptualization of humans and their ultramodern avatar. Posthumanism states that the future doesn't belong to human kind. Human may be replaced by robots, aliens or evolved, enhanced animals, isolation in the virtual world and digital sexuality.

The roots of feminist post humanism can be found in the early thoughts and works of Simone de Beauvoir, Helene Cixous, Jacques Derrida, Micheal Foucault, and also in feminist movement, studies and philosophy. Feminist post humanism theory separates the human from all those considered non-human. There is complex entanglement between humans and non-humans, machines, human animals. It made dualistic divisions and hierarchies between organism and machine, mind and body, nature and culture, human and animals, male and female.

Dystopia means an imagined world or society in which people lead wretched dehumanized and fearful lives. It is a very bad or unfair society in which there is a lot of suffering, especially an imaginary society in the future, after something terrible has happened. It is a literary device and genre used by writers to present a vision

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(सभी पद मानद एवं अवैतनिक हैं।)

शुल्क
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NEP 2020 and Multilingualism

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Macaulay's Minutes of 1835 and the Educational Dispatch of 1854on English education in India paved way to the learning of Englishlanguage and literature by Indians. Introduction of English degradedIndian languages to the position of mere 'vernaculars. GauriVishwanathan's book *Mask of Conquest* (1990) suggests that Englishliterary studies became a mask for economic and material exploitationand were an effective form of political control. The introduction ofEnglish studies was mainly intended at protection of British interests. Theearly generations of English educated Indians were contributing to theliterature in mother tongue using 'vernacular' for the expression of theinteriority and imagination while English was perceived as 'rational andfunctional tool for polemics and persuasion' (Mukherjee 9).

With theadvance of English education, 'English seeped into the intimate andpersonal domains of men of the elite classes' (Mukherjee 9). Still therehas been an 'anxiety of Indianness' (Mukharjee 166) which comes out ofIndian writer's effort to express an Indian experience through English.Raja Rao was the first Indian novelist who formulated the languageproblem that Indian writer had to face. In 'Foreword' to Kanthapura, he writes:

One has to convey in a language that is not one's owned thespirit that is one's own.One has to convey the variousshades and omissions of a certain thought movement thatlooks maltreated in an alien language. I use the word 'alien'yet English is not really an alien language to us. It is thelanguage of our intellectual make-up, like Sanskrit or Persianwas before – but not of our emotional make up. . . wecannot write like the English. (Rao i-ii)

However, the English language proliferated and penetrated into allaspects of civil strife through administration, profession, commerce,schooling, and media. However, infatuation with English is not withoutcultural strains. Use of English creates distance between theusers and their domestic and cultural mooring, alienating them fromtheir mother tongue.

English is the language of intellectual make up and the basis of elite formation in India. Teaching and learning in it resulted in a sense of alienationfrom Indian values and cultural structures, disaffection because languageis not only central to literary formulations but also to socio-political andcultural ones. Language is means of communication and a carrier ofculture. On the contrary, English is imposed on the natives to alienatethem from the self, relatives, and culture. Such alienation always

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Technology in Science Fiction: With Reference to "The Wall" by GautamBhatia and "Domechild" by Shiv Ramdas

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Abstract-
Literature is the reflection of life, culture, and society. It is the mirror of society that reflects the nature of human beings and nature. Writers try to express their ideas, emotions, thoughts, and feelings through literature. He communicates with the reader, through his writing. But as today's age is the age of science and technology, the trends of writing are changing. At the earlier stage of Indian English fictional writing, writers like Raja Rao, Mulk Raj Anand, and R .K. Narayan were mainly concerned with the Indian middle class, down- trodden people their life, problems, etc. At the time of Indian freedom; writers like Chaman Nahal, Arvind Ghosh, and Bankim Chandra Chatterjee wrote on the theme of the Indian Freedom Struggle, some writers wrote on partition and its effects on social and political problems, diasporic issues, postcolonialism, postmodernity and so on. But now the upcoming genre which is flourishing in Indian English Writing is Science Fiction known as SF. Writers like Vandana Singh, Shiv Ramdas, Sowmaya Rajendran, Gautam Bhatia, and many others have contributed to this The research scholar will try to explore the use of technology in Indian English science fiction regarding Gautam Bhatia's The Wall and Shiv Ramdas's Domechild.

Keywords: Science Fiction, Indian English Literature,

Introduction-

The everlasting cycle of progress creates complications, difficulties, and vague problems in the life of human beings. Inventions in science and technology are making a continuous change in the world and also the nature of literature. It makes an impact on the way of thinking, perceiving, interpreting, and also expressing through writing. Man becomes Techno-savvy, which taught him how to write, think, and communicate with others. It opens the window before human beings. It also develops communication between an author and the reader. Some years ago, book (reading material) is the only means of communication. Science and technology open many ways of communication and also change the nature and genres of literature. As literature is diverse, it adopts new styles from existing genres and inspires future generations of writers. In this 21st century, writers create genres like Mythopoeia, Bitpunk, Cli-Fi, Lucid Fiction, Twitter Novels, Interactive fiction, Bizarro, Fanfic, Chick-lit, Gran-lit, and Science Fiction, etc., and become quite popular over the past years and attract the attention of the reader.

Science fiction shortened as sci-fi or SF well-known as speculative fiction deals with imaginative and futuristic concepts such as advanced science and technology, space exploration, time travel, parallel universes, and extra-terrestrial life. The use of these elements increases the popularity of Science Fiction now this genre of literature become almost familiar to everyone. Some movies like Annihilation, The Girl with All the Gifts, The Maze Runner, Divergent, etc. are based on literary dystopia. The present research paper focuses on how technology has made a continued influence on literature concerning Indian English Writing.

Indian Science Fiction:

Indian science fiction has a long history from the times of the great Hindu Epics. Generally, it is accepted as a study of the impact of science and technology on mankind in India. But now Indian English SF writers focus on the theme of the future of India, and how scientific technology will make the lives of people comfortable in the cities like Mumbai, Delhi, and Kolkata, by giving it a dystopian side. They not only explore robotic stories, and alien encounters but also humanoid, supercomputers, biotechnological use, etc. through writing.

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