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Phytochemical and pharmacological potential of *Hydnocarpus wightianus* Blume: A comprehensive review

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Abstract

The chaulmoogra tree, or *Hydnocarpus wightianus* Blume, is a medicinally significant plant that is frequently used in traditional medical systems like Ayurveda and Siddha to treat leprosy, skin conditions, wounds, rheumatism, and inflammatory disorders. The phytochemical composition, pharmacological activity, therapeutic uses, toxicological characteristics, and future research prospects of *H. wightianus* are all thoroughly summarized in this paper. Flavonoids, flavonolignans, phenolic compounds, terpenoids, and cyclopentenyl fatty acids like hydnocarpic acid, chaulmoogric acid, and gorlic acid are among the plant's abundant biologically active phytoconstituents. These bioactive substances have a variety of pharmacological characteristics, such as antibacterial, antileprotic, antitubercular, antioxidant, anti-inflammatory, wound healing, and anticancer effects. Microbial membrane rupture, inflammatory mediator inhibition, reactive oxygen species scavenging, and cellular signalling pathway regulation are the primary mechanisms of action. Additionally covered are the historical and contemporary therapeutic uses of chaulmoogra oil for infectious and dermatological conditions. This review also emphasizes toxicological research, safety assessment, industrial significance, current research trends, and difficulties related to the use of *H. wightianus* in pharmaceuticals. The therapeutic potential of this plant has been further improved by recent developments in nanotechnology-based formulations and tailored drug delivery systems. Limitations like the toxicity of crude oil formulations, low absorption, and lack of clinical validation continue to be key issues despite its enormous medicinal promise. Therefore, to create safe, standardized, and efficient medicinal formulations from *H. wightianus*, more molecular, pharmacological, and clinical research is needed.

1. Introduction

Hydnocarpus wightianus Blume, a member of Achariaceae family is distributed across South and Southeast Asia, particularly in India, Sri Lanka, Myanmar, Thailand, Malaysia and Indonesia (Sahoo *et al*., 2014; Sharma *et al*., 2020). The species commonly occurs in tropical evergreen and semi-evergreen forests under warm and humid climatic conditions (Nadkarni, 2009). It is mainly found in the Western Ghats and other moist forest ecosystems with well-drained soils and high rainfall (Rastogi and Mehrotra, 2002). Because of their abundance of bioactive chemicals and therapeutic potential, medicinal plants continue to play an important role in healthcare systems around the world. The World Health Organization (WHO) reports that a sizable section of the world's population, especially in developing nations, depends on traditional herbal remedies for basic medical requirements. The growing need for natural goods, safer therapeutic agents, and alternative medications with fewer side effects than synthetic treatments has led to a significant surge in scientific interest in medicinal plants in recent years. In order to find novel chemicals with pharmaceutical importance, various medicinal plant species have been the subject of rigorous phytochemical and pharmacological experiments. Due to its varied biological activities and historical medicinal value, *H. wightianus* has drawn a lot of interest among the traditionally significant medicinal plants. Prior to the development of sulfone therapy, the plant's seeds yield chaulmoogra oil, which has long been known for its efficacy in treating leprosy and chronic skin conditions. Different portions of the plant have been widely used in traditional medical systems like Ayurveda and Siddha to treat microbiological disorders, rheumatism, ulcers, wounds, inflammation, and skin infections. The distinctive phytochemical profile of *H. wightianus* is the main factor contributing to its therapeutic significance. The plant's many pharmacological actions are attributed to flavonoids, tannins, alkaloids, saponins, glycosides, and phenolic chemicals in addition to these fatty acids. These secondary metabolites have strong antibacterial, antioxidant,

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anti-inflammatory, anticancer, and wound healing qualities, according to earlier phytochemical studies (Sharma *et al.,* 2020). The traditional use of seed extracts and oil formulations in infectious disorders has been supported by their notable antibacterial and antifungal properties against pathogenic microorganisms (Kumar *et al.,* 2017). Additionally, because the plant extracts include phenolic and flavonoid components, antioxidant tests have demonstrated their capacity to scavenge free radicals. Animal models have also shown anti-inflammatory and analgesic properties, suggesting the plant's potential for treating inflammatory conditions (Patil and Deshmukh, 2019). Information about the phytochemistry and pharmacological characteristics of *H. wightianus* is still dispersed over numerous scientific sources, despite the plant's significant traditional significance and new scientific findings. Therefore, a thorough and methodical examination is necessary to compile the existing information and offer a better comprehension of its therapeutic importance. The goal of this review is to provide a comprehensive overview of *H. wightianus* phytochemical components, pharmacological activities, traditional usage, extraction techniques, toxicological issues, and therapeutic applications. The review also covers future prospects and present research trends for the creation of plant based therapeutic medicines derived from this significant species for medicine.

2. Phytochemical constituents

The complex and varied phytochemical content of *H. wightianus* is directly linked to its medicinal relevance. Numerous secondary metabolites that have significant pharmacological effects on people and perform significant ecological roles are produced by medicinal plants. Cyclopentenyl fatty acids, flavonoids, alkaloids, tannins, phenolic compounds, glycosides, saponins, sterols, and fixed oils have all been found in *H. wightianus*, according to phytochemical analyses. These substances support the plant's antibacterial, antioxidant, analgesic, anti-inflammatory, wound healing, and antileprotic qualities (Muthaiyan *et al*., 2018; Sharma *et al*., 2020). Cyclopentenyl fatty acids are thought to be the most distinctive components of *H. wightianus* among the known phytochemicals. Rarely present in higher plants, these specific fatty acids have garnered significant interest due to their traditional medical uses, particularly in the treatment of leprosy and chronic skin conditions. The presence of many bioactive chemicals responsible for the plant's pharmacological activity has been established by contemporary phytochemical research using chromatographic and spectroscopic techniques (Singh *et al.,* 2017).

2.1 Cyclopentenyl fatty acids

Chaulmoogra oil, which is abundant in *H. wightianus* seeds, contains unique cyclic fatty acids known as cyclopentenyl fatty acids. The three main fatty acids found are gorlic acid, hydnocarpic acid, and chaulmoogric acid. These substances are regarded as Hydnocarpus genus chemotaxonomic indicators. The structural characteristic that gives hydnocarpic acid and chaulmoogric acid their distinct biological actions is the presence of a cyclopentene ring in their carbon chain (Rastogi and Mehrotra, 2002). Research has demonstrated that by disrupting microbial fatty acid metabolism, cyclopentenyl fatty acids have inhibitory effects against *Mycobacterium leprae* and other dangerous microbes (Brown and Hazen, 1940). These fatty acids also have antifungal and anti-inflammatory properties, according to recent pharmacological evaluations. Sharma *et al.* (2020) stated that while chaulmoogric acid aids in tissue repair and the decrease of inflammatory lesions, hydnocarpic acid exhibits bacteriostatic activity against gram-positive bacteria.

2.2 Flavonoids

Naturally occurring polyphenolic chemicals with antioxidant and medicinal qualities are called flavonoids. Various solvent extracts of *H. wightianus* leaves, bark, and seeds have tested positive for flavonoids during phytochemical screening (Kumar *et al*., 2017).

By scavenging free radicals and lowering oxidative stress, flavonoids mainly function as antioxidants. Numerous chronic conditions, including as cancer, diabetes, heart disease, and inflammation, are linked to oxidative damage. The antioxidant activity of *H. wightianus* extracts may therefore be linked to their flavonoid content. Additionally, a number of flavonoids have hepatoprotective, anti-ulcer, anticancer, and antibacterial qualities (Panche *et al*., 2016). According to recent evaluations, flavonoids stabilize connective tissues and prevent lipid peroxidation, which may promote collagen formation and wound healing processes. This validates the traditional application of *H. wightianus* for the treatment of dermatological conditions and wounds.

2.3 Alkaloids

Alkaloids are bioactive substances that contain nitrogen and are frequently linked to potent pharmacological effects. Alkaloids have been found in *H. wightianus* leaves and seeds, according to preliminary phytochemical research (Patil and Deshmukh, 2019). Alkaloids have a variety of therapeutic uses, such as analgesic, anti-inflammatory, antibacterial, antimalarial, and anticancer effects. The presence of some alkaloids from *H. wightianus* may greatly enhance the plant's medicinal effectiveness, despite the fact that these compounds have not been thoroughly isolated and described. Alkaloids frequently serve as defence molecules and may work in concert with other phytochemicals found in therapeutic plants, according to Harborne (1998).

2.4 Tannins and phenolic compounds

Important secondary metabolites with potent antibacterial and antioxidant properties are tannins and phenolic compounds. These substances have the ability to precipitate proteins and shield plant tissues from microbial invasion. *H. wightianus* extracts have demonstrated a significant total phenolic content, suggesting a potential involvement in disease prevention and free radical scavenging (Sharma and Kumar, 2018). By neutralizing reactive oxygen species (ROS), inhibiting lipid peroxidation, chelating metal ions, and suppressing inflammatory mediators, among other methods, phenolic substances have therapeutic effects. Tannins are thought to have antibacterial properties because they can block extracellular enzymes and damage microbial cell membranes. Additionally, research has shown that tannins speed up tissue regeneration and wound contraction, validating the traditional medical uses of *H. wightianus* (Cowan, 1999).

2.5 Saponins

Glycosidic substances called saponins are distinguished by their ability to foam like soap. Saponins have been found in *H. wightianus* methanolic and aqueous extracts through phytochemical analyses. The antibacterial, immunomodulatory, anti-inflammatory, and cholesterol lowering properties of saponins are well known (Francis *et al*., 2002).

According to research, saponins may increase membrane permeability and make it easier for other bioactive substances to be absorbed. They also show cytotoxic effects on several cancer cell lines, which may enhance the anticancer potential of medicinal herbs.

2.6 Glycosides

Comprising both sugar and non-sugar components, glycosides are physiologically active substances. Glycosides have been found in several sections of *H. wightianus* in preliminary screening investigations. It is well known that glycosides have anti-inflammatory, antibacterial, antioxidant, and cardioprotective qualities. Because of their therapeutic advantages, a number of medicinal plants that contain glycosides are frequently utilized in pharmaceutical formulations. Therefore, the traditional therapeutic uses of *H. wightianus* may be attributed to its glycosidic contents.

2.7 Sterols and terpenoids

Terpenoids and plant sterols are significant bioactive components with anti-inflammatory and membrane stabilizing properties. Terpenoids found in medicinal plants have demonstrated hepatoprotective, antiviral, and anticancer properties (Mahato and Sen, 1997). Sterols and terpenoid derivatives are present in *H. wightianus*, according to preliminary phytochemical research, though further characterisation is still lacking.

2.8 Fixed oils and lipid components

About 30-40% of *H. wightianus* seeds are fixed oil, also known as chaulmoogra oil. Triglycerides comprising hydnocarpic and chaulmoogric acids, as well as palmitic and oleic acids, make up the majority of the oil. Chaulmoogra oil’s therapeutic benefits have been well documented in colonial and traditional medical literature (Nadkarni, 2009).

Because of its emollient and antibacterial qualities, chaulmoogra oil has been studied for use in cosmetic formulations in addition to therapeutic uses. Its use in topical creams, nanoemulsions, and herbal dermatological products has been investigated in recent investigations. Extensive phytochemical research indicates that the synergistic interplay of several bioactive substances is responsible for *H. wightianus* medicinal efficacy. Numerous phytochemicals found in plants have been identified and characterized thanks to modern analytical techniques like gas chromatography-mass spectrometry (GC-MS), thin layer chromatography (TLC), high performance liquid chromatography (HPLC), fourier transform infrared spectroscopy (FTIR), and nuclear magnetic resonance (NMR). Natural compounds from *H. wightianus* may be viable substitutes for synthetic antibacterial and anti-inflammatory drugs, according to recent evaluations. To isolate novel chemicals, comprehend their molecular mechanisms, and assess their clinical safety and efficacy, more research is necessary. Future pharmaceutical development also depends on the standardization of extracts and the sustainable use of plant resources.

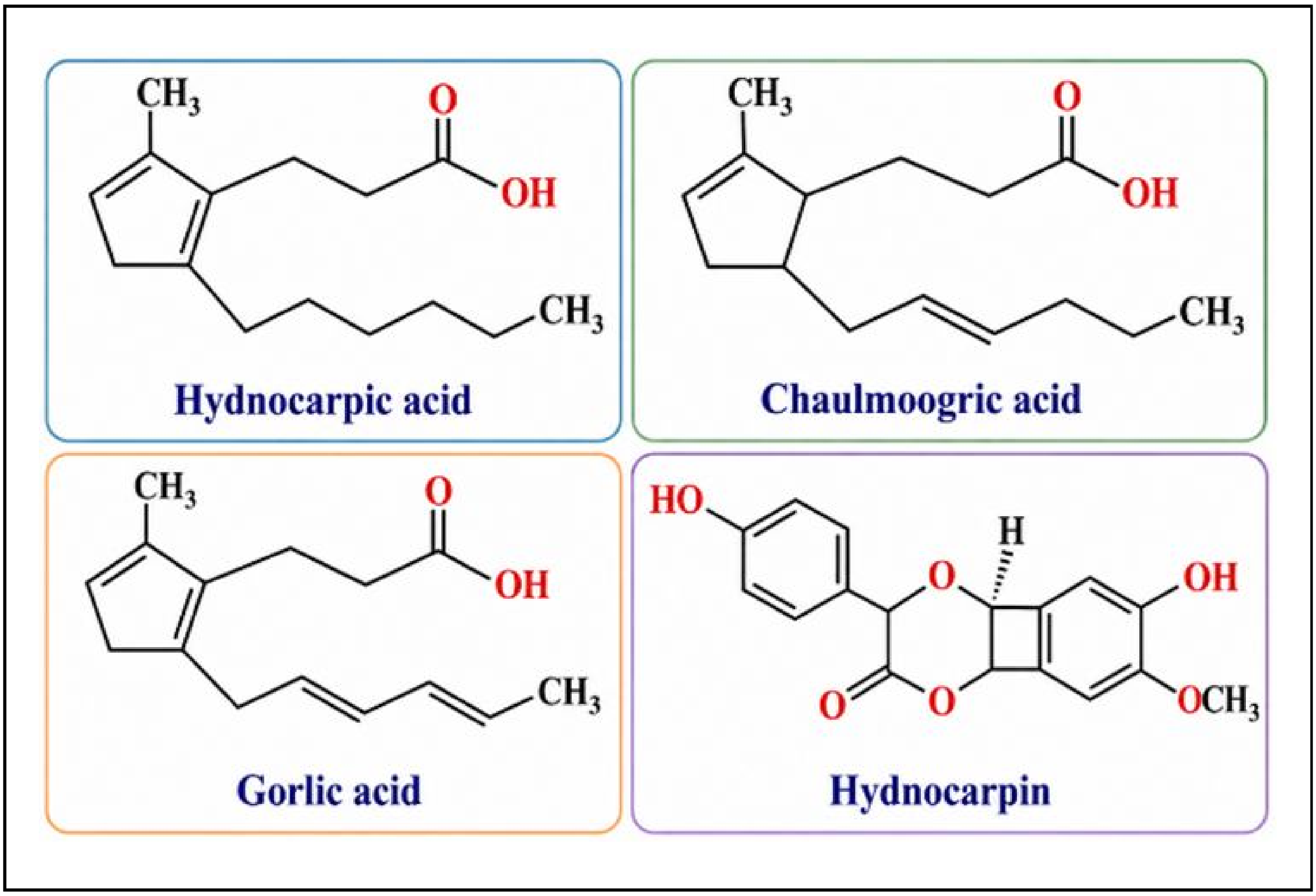

Figure 1: Chemical structures of major bioactive constituents.

3. Extraction and isolation techniques

Understanding the phytochemical profile and pharmacological potential of *H. wightianus* requires the extraction and isolation of bioactive substances. The goal of effective extraction techniques is to maximize the production of medicinally active components while maintaining their chemical integrity. The amount and quality of secondary metabolites found in the plant, such as cyclopentenyl fatty acids, flavonoids, phenolics, alkaloids, sterols, and glycosides, are greatly influenced by the extraction method chosen (Azmir *et al.,* 2013). Because of their high oil content, the seeds of *H. wightianus* are the most investigated component; polar bioactive chemicals are also found in the leaves and bark. Depending on the phytochemical class being targeted, this species has been extracted using both traditional and contemporary methods. While advanced techniques like ultrasound assisted extraction, microwave assisted extraction, and supercritical fluid extraction are increasingly preferred due to their efficiency and environmental benefits, conventional methods like maceration and Soxhlet extraction are still widely used for crude extraction (Chemat *et al.,* 2017; Herrero *et al*., 2010).

3.1 Conventional extraction methods

One of the easiest and most used extraction techniques for *H. wightianus* is maceration. This method involves soaking powdered plant material for a long time at room temperature in appropriate solvents such ethanol, methanol, or water. For the extraction of thermolabile substances like flavonoids and phenolics, this technique is especially helpful. Because of their high phenolic content, studies have shown that methanolic extracts of *H. wightianus* leaves and seeds produced by maceration have strong antioxidant and antibacterial action (Kumar *et al*., 2017). Nevertheless, compared to contemporary methods, maceration is time consuming and frequently yields lower extraction efficiency.

Lipophilic chemicals, particularly fixed oils from *H. wightianus* seeds, are frequently isolated by Soxhlet extraction. The process effectively recovers chaulmoogra oil through continuous extraction using hot solvents like hexane or petroleum ether. The oil's traditional antileprotic action is caused by biologically active cyclopentenyl fatty acids, such as hydnocarpic acid and chaulmoogric acid (Muthaiyan *et al*., 2018). Long term heating may deteriorate heat sensitive components even when Soxhlet extraction yields more. Although, *H. wightianus* is not a significant producer of essential oils, steam distillation is sometimes used to separate volatile components from leaves and bark. This technique minimizes thermal degradation of volatile chemicals by enabling extraction at comparatively low temperatures (Harborne, 1998).

3.2 Modern extraction techniques

The capacity of ultrasound assisted extraction to improve extraction efficiency through acoustic cavitation has drawn a lot of interest. By breaking down plant cell walls, this mechanism enhances solvent penetration and makes it easier for intracellular chemicals to be released. It has been demonstrated that ultrasound assisted extraction of medicinal plants increases the production of phenolics and flavonoids while decreasing extraction time and solvent consumption (Chemat *et al*., 2017). This method works especially well for extracting antioxidant rich leaves from *H. wightianus*.

Another cutting-edge method that uses microwave radiation to quickly heat solvents and plant matrices is microwave-assisted extraction. Better mass transfer and quicker bioactive chemical extraction are the outcomes of this. When compared to traditional techniques, microwave-assisted extraction has been shown to improve the recovery of phenolic chemicals in medicinal plants (Azmir *et al*., 2013). The extraction efficiency of both polar and non-polar phytochemicals may be increased by applying this method to H. *wightianus*. One of the most effective green extraction methods for non-polar chemicals is supercritical fluid extraction with carbon dioxide. It offers minimum environmental effect, low toxicity, and great selectivity. This technique works especially well for removing solvent residues from seed oils that are high in hydnocarpic and chaulmoogric acids (Herrero *et al.,* 2010). Supercritical fluid extraction is thought to be a potential technique for obtaining high purity chaulmoogra oil for medicinal uses in *H. wightianus*.

4. Isolation and purification techniques

For initial screening and phytochemical class identification in *H. wightianus*, thin layer chromatography is frequently utilized. It offers quick and affordable profiling of substances like fatty acids, alkaloids, and flavonoids. Individual substances can be separated from crude extracts using column chromatography based on variations in polarity and adsorption characteristics. Cyclopentenyl fatty acids have been separated from chaulmoogra oil fractions using this method (Singh *et al.,* 2017).

High performance liquid chromatography is a powerful analytical technique used for both phytochemical examinations, both qualitative and quantitative. HPLC has been utilized to accurately and consistently identify phenolic chemicals and fatty acid derivatives in *H. wightianus* (Sharma *et al*., 2020). In order to identify hydnocarpic acid, chaulmoogric acid, palmitic acid, and oleic acid, GC-MS is often used to profile the volatile and semi-volatile components in chaulmoogra oil. Plant extracts can have their functional groups identified and the presence of carboxylic acids, esters, and hydroxyl groups confirmed using Fourier transform infrared spectroscopy. Clarifying the molecular structure of isolated cyclopentenyl fatty acids and similar compounds requires the use of nuclear magnetic resonance spectroscopy, which offers comprehensive structural information.

The recovery and characterisation of bioactive chemicals from medicinal plants have been greatly enhanced by recent developments in extraction technology. Due to their effectiveness, lower solvent consumption, and environmental safety, green extraction techniques such supercritical fluid extraction, microwave assisted extraction, and ultrasound assisted extraction are gradually taking the place of traditional methods. These contemporary methods are very useful for generating phenolic rich extracts and superior chaulmoogra oil in *H. wightianus*. Numerous investigations have shown that the extraction method employed has a significant impact on the biological activity of *H. wightianus* extracts since different methods produce distinct phytochemical profiles. To improve the isolation of pharmacologically active molecules, bioassay guided extraction techniques have also been suggested. Standardized extraction procedures, process parameter optimization, and large-scale industrial applications are still required, despite tremendous advancements. In order to increase the yield, purity, and repeatability of phytochemical contents, future research should concentrate on combining cutting-edge analytical methods with environmentally friendly extraction technologies. Additionally, more research is needed to investigate the molecular mechanisms of action and synergistic interactions among isolated drugs

5. Pharmacological activities

Because *H. wightianus* has a long history in traditional medicine, especially in the Ayurvedic and Siddha systems, its pharmacological potential has been thoroughly studied over the past few decades. This plant's extensive phytochemical composition particularly cyclopentenyl fatty acids, flavonoids, phenolics, tannins, alkaloids, saponins, and sterols is largely responsible for its biological activity. A wide range of therapeutic effects, such as antimicrobial, anti-inflammatory, antioxidant, antileprotic, antidiabetic, anticancer, analgesic, wound healing, and immunomodulatory activities, are produced by these compounds' individual and combined actions (Sharma *et al*., 2020; Panche *et al.,* 2016).

5.1 Antimicrobial activity

One of *H. wightianus* most well-established pharmacological characteristics is its antibacterial activity. Fungal pathogens, gram-positive bacteria, and gram-negative bacteria have all been demonstrated to be inhibited by seed oil and different solvent extracts. By rupturing microbial cell membranes and interfering with lipid manufacturing pathways necessary for microbial survival, cyclopentenyl fatty acids like hydnocarpic acid and chaulmoogric acid play a crucial part in this action. By blocking quorum sensing, energy metabolism, and nucleic acid production, flavonoids and phenolic chemicals further strengthen antimicrobial actions. By precipitating microbial proteins and blocking extracellular enzymes necessary for the advancement of infection, tannins play a role (Cowan, 1999; Scalbert, 1991). Additionally, recent research indicates that fatty acids produced from plants may function as efflux pump inhibitors, making bacteria more vulnerable to antimicrobial drugs (Borges *et al*., 2016).

5.2 Anti-inflammatory activity

H. wightianus ability to reduce inflammation is mostly achieved by blocking inflammatory mediators such prostaglandins, cytokines, and nitric oxide. Because cyclooxygenase (COX) enzymes are inhibited by cyclopentenyl fatty acids, prostaglandins that cause pain and inflammation are produced at a lower rate. The plant's flavonoids inhibit the NF-κB signalling system, which controls the expression of pro-inflammatory genes like TNF-α, IL-1β, and IL-By scavenging reactive oxygen species, which are known to initiate inflammatory cascades, phenolic substances further reduce inflammation (García-Lafuente *et al*., 2009; Reuter *et al*., 2010). The herb has long been used to treat chronic illnesses and inflammatory skin diseases thanks to these combined methods.

5.3 Antioxidant activity

H. wightianus most important pharmacological characteristics is antioxidant activity, which is mainly due to the plant's high flavonoid and phenolic component concentration. By giving electrons or hydrogen atoms to free radicals, these bioactive compounds stop oxidative damage to proteins, lipids, and DNA. Additionally, flavonoids bind metal ions like copper and iron, which cause Fenton reactions that produce extremely reactive hydroxyl radicals. Because of this dual activity, *H. wightianus* extracts are useful in lowering oxidative stress related illnesses such cancer, diabetes, and cardiovascular conditions (Halliwell and Gutteridge, 2015; Dai and Mumper, 2010).

5.4 Antileprotic activity

Leprosy treatment is one of *H. wightianus* most important historical applications. Before the advent of contemporary multidrug therapy, chaulmoogra oil, which was derived from its seeds, was frequently used. The primary cause of the antileprotic action is cyclopentenyl fatty acids, which are selectively poisonous to *M. leprae*. These fatty acids prevent bacterial development by interfering with the formation of mycolic acid, a crucial part of the mycobacterial cell wall. Furthermore, flavonoids and saponins' immunomodulatory properties may strengthen host immunological responses and aid in the prevention of infection (Rastogi and Mehrotra, 2002; Brown and Hazen, 1940).

5.5 Anticancer activity

H. wightianus extracts have been shown in recent research to have anticancer potential through a variety of pathways. By triggering caspase-dependent pathways and controlling the Bax/Bcl-2 ratio, flavonoids cause cancer cells to undergo apoptosis. By lowering oxidative DNA damage and inhibiting inflammatory signalling pathways, phenolic substances prevent the development and spread of tumours. Additionally, cyclopentenyl fatty acids may interfere with energy metabolism and damage the integrity of cancer cell membranes. Additionally, bioactive chemicals originating from plants have been shown to block angiogenesis and cause cell cycle arrest at various stages in experimental models (Aggarwal *et al*., 2006; Liu, 2014).

5.6 Antidiabetic activity

H. wightianus antidiabetic action is mostly linked to the suppression of enzymes that break down carbohydrates, including á-amylase and á-glucosidase. As a result, postprandial hyperglycaemia is decreased and glucose absorption is delayed. By increasing GLUT4 translocation, flavonoids increase insulin sensitivity and encourage glucose absorption in peripheral tissues. Additionally, phenolic substances improve insulin production and glycaemic management by shielding pancreatic â-cells from oxidative stress induced damage (Tundis *et al.,* 2010; Panche *et al*., 2016).

5.7 Analgesic activity

H. wightianus is thought to have analgesic effects via inhibiting cyclooxygenase enzymes, which suppress prostaglandin synthesis. While flavonoids influence both cerebral and peripheral pain pathways, cyclopentenyl fatty acids decrease peripheral pain signals.

The historic usage of the plant to treat arthritis, inflammatory pain, and skin irritation is supported by these mechanisms (Vane and Botting, 1998; Patil and Deshmukh, 2019).

5.8 Immunomodulatory activity

Increased collagen synthesis, fibroblast proliferation, and epithelialization promote wound healing activity. By lowering oxidative stress and promoting the synthesis of growth factors, flavonoids and phenolic substances hasten tissue regeneration. Tannins help by encouraging tissue contraction and creating a barrier over wounds. Furthermore, fatty acids' antibacterial qualities speed up the healing process by preventing infection (Gurtu *et al*., 2007; Singh *et al*., 2017).

6. Integrated pharmacological perspective

Several phytochemical classes work in concert to produce the pharmacological effects of *H. wightianus*. Polyphenols and flavonoids play a major role in antioxidant, anti-inflammatory, anticancer, and antidiabetic actions, while fatty acids are principally responsible for antibacterial and antileprotic activities. The plant is a prospective candidate for multi-disease therapeutic applications because of its multitarget mechanism of action, which modulates NF-κB, COX, MAPK, oxidative stress pathways, and apoptotic signalling cascades (Sharma *et al.,* 2020; Reuter *et al.,* 2010).

6.1 Mechanism of action of bioactive compounds

Through a variety of biochemical and molecular mechanisms, recent phytochemical and pharmacological research has shown that the bioactive compounds of *H. wightianus* have antibacterial, antileprotic, anti-inflammatory, antioxidant, antitubercular, and anticancer properties (Sahoo *et al*., 2014; Naikawadi *et al.,* 2023). According to Rameshkumar *et al.* (2011), these bioactive substances primarily work by rupturing microbial membranes, modifying inflammatory pathways, scavenging free radicals, and causing aberrant cells to undergo apoptosis.

Cyclopentenyl fatty acids, such as hydnocarpic acid, chaulmoogric acid, and gorlic acid, are the main phytochemicals found in *H. wightianus* and are thought to be the main medicinal components of chaulmoogra oil (Spener and Mangold, 1975). Furthermore, phenolic compounds, flavonoids, sterols, volatile terpenoids like á-pinene and â-pinene, and flavonolignans like hydnocarpin and neohydnocarpin have all been documented (Sahoo *et al*., 2014; Schäfer *et al.,* 2025). These substances work in concert to support the plant's wide range of pharmacological actions.

6.2 Antileprotic mechanism

The primary cause of *H. wightianus* antileprotic action is cyclopentenyl fatty acids. By interfering with the manufacture of mycolic acids, which are vital components of the bacterial cell wall, hydnocarpic acid and chaulmoogric acid affect *M. leprae's* lipid metabolism (Sahoo *et al*., 2014). According to a different theory, chaulmoogra fatty acids boost macrophage activity and encourage mycobacteria phagocytosis, which in turn boosts host immunological responses (Rameshkumar *et al.,* 2011). Additionally, the fatty acids may trigger lipolytic enzymes that break down bacterial lipids, making it easier for the immune system to eliminate *M. leprae* (Behl and Srivastava, 2002).

6.3 Antitubercular mechanism

Mycobacterium tuberculosis has been demonstrated to be inhibited by hydnocarpic acid and similar fatty acids (Naikawadi *et al*., 2023). The mechanism entails the suppression of fatty acid production pathways necessary for bacterial growth and survival as well as the breakdown of membrane integrity. Cyclopentenyl fatty acids cause intracellular component leakage and ultimately bacterial death by interfering with membrane associated enzymes involved in respiration and energy synthesis (Lima *et al.,* 2005).

6.4 Antibacterial mechanism

Terpenoid components and cyclopentenyl fatty acids are responsible for *H. wightianus* antibacterial action. By changing the structure of phospholipid bilayers and raising membrane permeability, these substances damage bacterial cell membranes (Schäfer *et al.,* 2025). Bacterial cell lysis is eventually caused by the leakage of cellular ions, proteins, and nucleic acids. By blocking membrane bound ATPase enzymes and obstructing electron transport mechanisms, monoterpenes like α-pinene and β-pinene further strengthen antibacterial activities (Duraipandiyan *et al.,* 2006). Research has demonstrated efficacy against gram-positive and gram-negative bacteria, such as *B. subtilis, E. coli*, and *S. aureus* (Sahoo *et al.,* 2014).

6.5 Anti-inflammatory mechanism

By inhibiting inflammatory mediators including prostaglandins, nitric oxide, and cytokines, flavonoids, phenolic compounds, and fatty acids found in *H. wightianus* have anti-inflammatory properties (Sahoo *et al.,* 2014). These substances inhibit the lipoxygenase (LOX) and cyclooxygenase (COX) enzyme pathways that produce inflammatory eicosanoids (Shahid and Mohammad, 2013). By scavenging reactive oxygen species (ROS), phenolic antioxidants also lessen oxidative stress by preventing the activation of NF-êB signaling pathways linked to chronic inflammation (Yusuf *et al.,* 2017). This process helps explain why chaulmoogra oil has long been used to treat rheumatic and inflammatory skin diseases.

6.6 Antioxidant mechanism

Flavonoids and phenolic compounds in *H. wightianus* use electron donation and hydrogen atom transfer to neutralize free radicals (Yusuf *et al.,* 2017). These antioxidants prevent oxidative damage to proteins, lipids, and nucleic acids by inhibiting lipid peroxidation.

By boosting the activity of antioxidant enzymes including glutathione peroxidase, catalase, and superoxide dismutase, terpenoids and flavonoids may help improve endogenous antioxidant defence mechanisms (Shahid and Mohammad, 2013). This antioxidant characteristic may be very important in preventing degenerative and inflammatory illnesses.

6.7 Anticancer mechanism

By altering tumour cells' pathways of multidrug resistance, hydnocarpin, a flavonolignan extracted from Hydnocarpus species, has shown anticancer action (Sahoo *et al*., 2014). Hydnocarpin increases the intracellular accumulation of chemotherapeutic drugs and amplifies their lethal effects by blocking P-glycoprotein-mediated drug efflux. Through mitochondrial malfunction, caspase enzyme activation, and cell cycle arrest at various stages, flavonoids and phenolic chemicals found in *H. wightianus* may also cause apoptosis (Naikawadi *et al*., 2023). By lowering oxidative DNA damage, antioxidant activity also aids in chemoprevention.

7. Toxicological studies and safety evaluation

Because chaulmoogra oil is widely used medicinally in traditional medical systems, toxicological study of *H. wightianus* is crucial. Despite the plant's strong antibacterial, antileprotic, and anti-inflammatory properties, a number of studies have found negative effects linked to extended administration and crude oil formulations (Sahoo *et al.,* 2014). Both medicinal and toxicological effects are caused by the main bioactive components, especially cyclopentenyl fatty acids like hydnocarpic acid and chaulmoogric acid (Spener and Mangold, 1975). High doses of chaulmoogra oil have been linked to gastrointestinal discomfort, nausea, vomiting, and diarrhoea due to fatty acid components irritating the stomach mucosa, according to acute toxicity tests (Naikawadi *et al*., 2023). Additionally, at high dosages, experimental animal investigations showed mild hepatotoxicity and nephrotoxicity, indicating metabolic stress on liver and kidney tissues (Kishan *et al*., 2016). Particularly when used historically to treat leprosy, repeated administration of crude oil formulations has been linked to fever, weakness, and inflammatory reactions (Behl and Srivastava, 2002).

Chaulmoogra oil's highly lipophilic fatty acids and terpenoid components can induce skin irritation, erythema, and allergic dermatitis in sensitive people when applied topically (Rameshkumar *et al*., 2011). Due to the oil's high viscosity and poor solubility, injectable formulations have historically produced granulomatous inflammation, discomfort, and abscess formation (Sahoo *et al*., 2014). On the other hand, modified formulations such ethyl esters and refined extracts shown decreased toxicity and increased tolerance (Naikawadi *et al*., 2023). Standardized *H. wightianus* formulations appear to be rather safe at controlled therapeutic doses not with standing these side effects. While reducing irritation and systemic toxicity, contemporary pharmaceutical techniques including encapsulated delivery systems and nanoformulations may further enhance safety and bioavailability. To create uniform dosage recommendations and long-term safety profiles, however, thorough chronic toxicity, genotoxicity, and clinical safety studies are still needed.

Table 1: Summary of toxicological studies and safety assessment of *H. wightianus*

Toxicological parameter	Observation	Experimental model	References
Acute toxicity (LD_{50} value)	Specific LD_{50} values for *H. wightianus* extracts or chaulmoogra oil are not adequately reported in available literature	Not sufficiently documented	Kishan *et al.*, 2016; Naikawadi *et al.*, 2023
Dose associated toxicity	Exact toxic dose ranges are inadequately established; adverse effects mainly reported with prolonged administration of crude chaulmoogra oil formulations	Traditional use reports and experimental observations	Behl and Srivastava, 2002; Sahoo *et al.*, 2014
Experimental animal models	Preliminary toxicological evaluation conducted mainly in rodents	Rats and mice	Kishan *et al.*, 2016
Hepatotoxicity	Mild hepatotoxic responses observed under prolonged exposure/elevated doses	Experimental animal observations	Kishan *et al.*, 2016
Biochemical alterations	Elevated liver function indicators	Rodent models	Kishan *et al.*, 2016
Nephrotoxicity	Mild renal toxicity reported at higher exposure levels	Experimental animal observations	Kishan *et al.*, 2016
Histopathological changes (liver)	Mild hepatic tissue alterations	Animal studies	Kishan *et al.*, 2016
Histopathological changes (kidney)	Structural changes in renal tissues under prolonged exposure	Animal studies	Kishan *et al.*, 2016
Dermal toxicity	Topical adverse reactions occasionally reported	Human observations/ traditional applications	*Rameshkumar et al.*, 2011
Injectable formulation toxicity	Historical injectable chaulmoogra preparations showed local complications	Clinical historical use	Sahoo *et al.*, 2014
Improved formulations	Nanoformulations and refined ester preparations reduce adverse effects	Pharmaceutical formulations	Naikawadi *et al.*, 2023

7.1 Therapeutic applications in traditional and modern medicine

It is a significant medicinal plant that is widely used to treat leprosy, skin conditions, wounds, rheumatism, and inflammatory diseases in Ayurveda, Siddha, and traditional folk medicine (Sahoo *et al*., 2014; Rameshkumar *et al*., 2011). Prior to the creation of contemporary antibiotics. In traditional medicine, seed oil and paste preparations were commonly applied externally for due to their antibacterial and wound healing qualities, eczema, psoriasis, ulcers, scabies, and persistent skin infections (Mudaliar, 1936; Sharma and Hall, 1991). Additionally, chaulmoogra formulations were suggested by Siddha practitioners for parasite infections, pneumonia, constipation, and arthritis (Chellappandian *et al*., 2012). In chronic dermatological problems, the oil was thought to enhance tissue regeneration, lower inflammation, and purify blood.

Numerous conventional claims have been confirmed by contemporary pharmacological research, which has also shown that *H. wightianus* has antibacterial, antifungal, antileprotic, antitubercular, antioxidant, and anticancer properties (Naikawadi *et al*., 2023; Sahoo *et al*., 2014). By interfering with bacterial lipid metabolism and membrane integrity, cyclopentenyl fatty acids prevent the growth of *M. leprae* and *M. tuberculosis* (Lima *et al*., 2005). Antimicrobial action against *S. aureus, E. coli*, and fungal infections was also documented in experimental experiments (Duraipandiyan *et al*., 2006). By scavenging reactive oxygen species and inhibiting inflammatory mediators like prostaglandins and cytokines, flavonoids, phenolics, and terpenoids found in *H. wightianus* greatly contribute to antioxidant and anti-inflammatory activities (Yusuf *et al.*, 2017; Shahid and Mohammad, 2013). By increasing tumour cells' sensitivity to chemotherapeutic drugs by blocking multidrug resistance pathways, hydnocarpin, a flavonolignan derived from Hydnocarpus species, has demonstrated potential anticancer action (Sahoo *et al.*, 2014). Through the creation of nanoemulsions, ointments, encapsulated formulations, and transdermal delivery systems, recent pharmaceutical research has concentrated on enhancing the therapeutic efficacy and safety of chaulmoogra oil (Naikawadi *et al*., 2023). These cutting-edge formulations could improve patient compliance, lessen discomfort, and increase bioavailability. As a result, *H. wightianus* is still a valuable medicinal resource with significant applications in both conventional medical procedures and contemporary drug research.

Table 2: Phytochemical constituents, extraction approaches and pharmacological activities of *H. wightianus*

Plant part	Extraction method	Extraction solvent	Phytochemicals identified	Pharmacological activity	Experimental pathogen/model	References
Seeds (Chaulmoogra oil)	Soxhlet extraction	Hexane, petroleum ether	Hydnocarpic acid, chaulmoogric acid, gorlic acid (cyclopentenyl fatty acids)	Antileprotic	*M. leprae*	Brown and Hazen 1940; Rastogi and Mehrotra, 2002; Sahoo *et al.*, 2014
Seeds (oil extract)	Soxhlet extraction	Hexane/petroleum ether	Cyclopentenyl fatty acids	Antitubercular	*M. tuberculosis*	Lima *et al*., 2005; Naikawadi *et al.*, 2023
Seeds	Maceration	Methanol	Flavonoids, phenolics, tannins	Antioxidant	Free radical scavenging/ROS model	Kumar *et al.*, 2017; Halliwell and Gutteridge 2015; Dai and Mumper, 2010
Leaves	Maceration	Methanol	Flavonoids, phenolics, saponins	Antioxidant	Oxidative stress/ ROS model	Kumar *et al.*, 2017; Panche *et al.*, 2016; Sharma and Kumar, 2018
Leaves	Ultrasound-assisted extraction	Methanol/aqueous solvents	Flavonoids, phenolics	Anti-inflammatory	COX, NF-κB and cytokine inhibition models	García-Lafuente *et al*., 2009; Reuter *et al.*, 2010; Chemat *et al.*, 2017
Seeds	Maceration	Methanol	Flavonoids, tannins, phenolics	Antimicrobial	*S. aureus*, *E. coli*	Kumar *et al.*, 2017; Cowan, 1999; Scalbert, 1991
Seeds (oil fraction)	Soxhlet extraction	Hexane	Hydnocarpic acid, chaulmoogric acid	Antibacterial	*B. subtilis*, *S. aureus*, *E. coli*	Sahoo *et al*., 2014; Duraipandiyan *et al*., 2006; Sharma *et al.*, 2020
Leaves and bark	Maceration	Ethanol/methanol	Alkaloids, flavonoids, glycosides	Analgesic	Experimental inflammatory pain models	Patil and Deshmukh, 2019; Vane and Botting, 1998
Seeds	Conventional extraction	Fixed oil	Fatty acids, phenolics	Wound healing	Wound contraction and epithelialization models	Gurtu *et al.*, 2007; Singh *et al.*, 2017; Behl and Srivastava, 2002
Seeds	GC-MS profiling	Methanol	Fatty acids, flavonoids, terpenoids	Antidiabetic	α-amylase and α-glucosidase inhibition assay	Kathiresan *et al.*, 2024; Tundis *et al*., 2010; Panche *et al.*, 2016
Seeds	Column chromatography/HPLC purification	Solvent fractionation	Hydnocarpin, flavonolignans	Anticancer	Tumour cell apoptosis/MDR models	Aggarwal *et al.*, 2006; Liu, 2014; Sahoo *et al.*, 2014
Leaves and seeds	Microwave/ultrasound-assisted extraction	Polar solvents	Phenolics, flavonoids, terpenoids	Immunomodulatory	Immune stimulation /inflammatory response models	Francis *et al.*, 2002; Reuter *et al.*, 2010; Chemat *et al.*, 2017

8. Industrial and pharmaceutical importance

Because its seed oil and other plant parts contain biologically active cyclopentenyl fatty acids, flavonoids, and terpenoids, the chaulmoogra tree has significant industrial and pharmacological value (Sahoo *et al.,* 2014). The plant is a valuable resource for antimicrobial drug research since the oil's hydnocarpic acid and chaulmoogric acid have strong antimycobacterial action against *M. leprae* and *M. tuberculosis* (Spener and Mangold, 1975). Chaulmoogra oil has been used in the pharmaceutical sector to create injectable formulations for dermatological uses as well as ointments, lotions, soaps, and emulsions (Naikawadi *et al*., 2023). In order to increase the bioavailability, stability, and therapeutic efficacy of chaulmoogra oil while lowering irritation and toxicity, contemporary pharmaceutical research has concentrated on creating nanoemulsions, liposomal systems, and encapsulated formulations (Sahoo *et al*., 2014). The anticancer and multidrug resistance modulating properties of flavonolignans, such hydnocarpin, have also drawn interest, suggesting possible uses in cancer chemotherapy (Lima *et al*., 2005).

Because of its antibacterial, antioxidant, and skin protective qualities, chaulmoogra oil has been used in cosmetic and personal care products (Rameshkumar *et al*., 2011). Soaps, medicinal creams, and herbal skincare products for wound healing, eczema, and acne all contain the oil. Furthermore, because of its medicinal qualities, the fatty acid rich oil may find use in herbal formulations and nutraceuticals (Kishan *et al.,* 2016). The commercial value of *H. wightianus* has expanded due to recent interest in plant-based medicines and natural goods. Its industrial exploitation for the creation of innovative antimicrobial, anti-inflammatory, and dermatological treatments may be improved by sustainable use and cutting-edge biotechnological techniques.

9. Current research trends and future perspectives

The development of sophisticated drug delivery technologies, pharmacological validation, and phytochemical characterisation have been the key areas of recent research on *H. wightianus*. Using both *in vitro* and *in silico* methods, recent studies have shown that *H. wightianus* seed extracts contain antibacterial, antioxidant, anti-inflammatory, and antidiabetic properties (Kathiresan *et al.,* 2024; Sahoo *et al.,* 2014). Several bioactive compounds with antibacterial activity against methicillin resistant *S. aureus* (MRSA) and inhibitory action against α-amylase and α-glucosidase enzymes important in diabetes control were found by GC-MS research (Kathiresan *et al*., 2024). In order to increase the bioavailability, stability, and therapeutic efficacy of chaulmoogra oil and other plant derived chemicals, current pharmaceutical research also focuses on nanoformulations and nanocarrier based delivery methods. Because they improve medication penetration, lessen irritation, and limit toxicity related to crude oil formulations, nanoemulsions, liposomes, and nanostructured lipid carriers are being studied more and more (Naikawadi *et al*., 2023; Singh *et al.,* 2024). These sophisticated formulations could greatly enhance *H. wightianus* dermatological and antibacterial applications. The application of *H. wightianus* bioactive substances in treatments for skin regeneration and wound healing is another significant area of research. In chronic wounds and skin infections, herbal nanoformulations containing fatty acids and terpenoids have demonstrated encouraging anti-inflammatory, antibacterial, and tissue regenerative qualities (Agrawal *et al.,* 2024). Furthermore, the anticancer activity and modification of multidrug resistance in tumour cells of flavonolignans such hydnocarpin are being studied (Sahoo *et al*., 2014). In depth molecular mechanism investigations, toxicological assessment, clinical validation, and the sustainable synthesis of bioactive chemicals from *H. wightianus* are all potential avenues for future research. The plant's medical potential may be further enhanced by cutting-edge technologies including metabolomics, molecular docking, AI assisted drug discovery, and targeted nanotherapeutics (Stevanoviæ and Filipoviæ, 2024). Long term industrial and pharmaceutical usage of Hydnocarpus species also depends on conservation measures and sustainable use.

10. Challenges and limitations

Despite *H. wightianus* substantial pharmacological potential, a number of obstacles and restrictions prevent its widespread use in medicine and industry. Due to habitat degradation, overexploitation, and low natural regeneration, one of the main constraints is the restricted availability and poor conservation status of Hydnocarpus species (Sahoo *et al*., 2014). Therefore, to guarantee the ongoing supply of plant materials for pharmaceutical and therapeutic uses, sustainable farming and conservation techniques are required. The toxicity and irritation of crude chaulmoogra oil formulations present another significant obstacle. Due to the high content of cyclopentenyl fatty acids and poor solubility of the oil, traditional formulations frequently caused gastrointestinal disorders, skin irritation, inflammatory reactions, and injection site problems (Behl and Srivastava, 2002; Naikawadi *et al.,* 2023). Following the creation of safer synthetic medications, these side effects restricted chaulmoogra therapy's broad clinical acceptability. Another significant obstacle is the standardization of phytochemical makeup. Geographical location, climate, extraction technique, and plant maturity all affect the concentration of bioactive substances such hydnocarpic acid and chaulmoogric acid (Rameshkumar *et al.,* 2011). The safety, effectiveness, and repeatability of herbal formulations are impacted by the absence of regulated extraction and quality control procedures. Clinical trial based scientific validation is still insufficient. There are few thorough clinical trials verifying therapeutic efficacy and long-term safety in people, despite the fact that a number of *in vitro* and animal studies have shown encouraging antibacterial, anti-inflammatory, and antioxidant activity (Kishan *et al.,* 2016). Furthermore, many phytochemicals' precise molecular mechanisms of action are still poorly known. Pharmaceutical formulation is further complicated by the low bioavailability and poor water solubility of chaulmoogra oil components (Naikawadi *et al.,* 2023). To get beyond these restrictions and enhance treatment efficacy, cutting-edge delivery methods including liposomal formulations and nanoemulsions are presently being investigated. Furthermore, the economic use of *H. wightianus* in contemporary pharmaceutical enterprises is constrained by limited commercial cultivation, low awareness, and a lack of industrial scale processing technology. To fully realize *H. wightianus* therapeutic promise, future research should concentrate on conservation biology, systematic phytochemical analysis, sophisticated drug delivery technologies, toxicity assessment, and extensive clinical validation.

11. Conclusion

H. wightianus is a valuable medicinal plant with a broad range of pharmacological potential and a notable diversity of phytochemicals. In addition to flavonoids, flavonolignans, phenolics, and terpenoids that support the plant's medicinal qualities, it is especially rich in physiologically active cyclopentenyl fatty acids like hydnocarpic acid, chaulmoogric acid, and gorlic acid. In addition to proving that *H. wightianus* has antibacterial, antileprotic, antitubercular, antioxidant, anti-inflammatory, wound healing, and anticancer properties, contemporary scientific research has confirmed a number of traditional claims. Disruption of microbial membranes, suppression of inflammatory mediators, scavenging of reactive oxygen species, and modification of cellular signalling pathways are the primary mechanisms by which the pharmacological activities are mediated. The medicinal potential of chaulmoogra oil and its bioactive components have been further enhanced by recent developments in nanotechnology and drug delivery technologies. Despite its significant therapeutic value, a number of issues still exist, such as the toxicity of crude oil preparations, poor aqueous solubility, a lack of standardized formulations, and scant clinical validation. Large scale medicinal use may also be limited by inadequate conservation measures and variations in phytochemical makeup. In order to improve safety and efficacy, future research should concentrate on thorough molecular mechanism investigations, toxicological assessment, clinical trials, sustainable cultivation, and the creation of cutting-edge pharmaceutical formulations. Overall, *H. wightianus* represents a promising source of bioactive compounds with substantial therapeutic and industrial potential. The creation of new plant based therapeutic compounds from this important medicinal species may be made possible by ongoing multidisciplinary research combining phytochemistry, pharmacology, biotechnology, and nanomedicine.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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