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MEDICINAL CHEMISTRY OF DALBERGIA SISSOO (SHEESHAM TREE) AND ITS ADVANCED APPLICATIONS IN THE DRUG INDUSTRY

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ABSTRACT

Dalbergia sissoo DC., commonly known as Sheesham or North Indian Rosewood, is a fast-growing deciduous tree with a rich history in traditional medicine. This report provides a comprehensive overview of its botanical characteristics, extensive ethnobotanical uses, and its significant phytochemical profile, which includes a diverse array of compounds such as flavonoids, alkaloids, terpenoids, and phenolics. Scientific investigations have validated numerous pharmacological activities, including potent anti-inflammatory, analgesic, antidiabetic, anticancer, osteogenic, and neuroprotective effects, often elucidated through specific molecular mechanisms. Recent advancements in drug formulation, such as the development of ethosomal gels and nanoparticles, are enhancing the bioavailability and targeted delivery of *D. sissoo* compounds. While preliminary safety studies indicate a favorable profile, further comprehensive pharmacokinetic, genotoxicity, and long-term clinical trials are imperative. The report highlights the critical role of robust standardization and sustainable sourcing practices to ensure the quality and long-term viability of *D. sissoo* as a valuable resource for novel drug development within the pharmaceutical industry.

1. INTRODUCTION

1.1. Botanical Classification and Characteristics of *Dalbergia sissoo*

Dalbergia sissoo DC., widely recognized as Sheesham, North Indian Rosewood, or Sissoo, holds a distinguished position within the plant kingdom. Botanically, it is classified under Kingdom Plantae, Division Magnoliophyta, Class Magnoliopsida, Order Fabales, Family Fabaceae (also known as the bean or legume family), Genus *Dalbergia*, and Species *sissoo*. This classification places *D. sissoo* within a family renowned for its rich diversity of secondary metabolites, many of which possess significant biological activities.

The tree is a fast-growing, hardy, and deciduous species, native to the Indian subcontinent and extending into southern Iran. Its natural habitat primarily spans tropical to subtropical climates, often found along river banks at elevations above 200 meters, though it can naturally range up to 1,400 meters. This plant exhibits remarkable adaptability, thriving in a wide temperature range from just below freezing to nearly 50°C and tolerating average annual rainfall up to 2,000 millimeters, including droughts lasting three to four months. This inherent hardiness and ability to flourish across varied environmental conditions are significant attributes. Such ecological resilience suggests that *D. sissoo* is not ecologically fragile or overly demanding in its growth requirements, which is a critical advantage for sustainable sourcing in the drug industry. Plants that can be cultivated efficiently across diverse geographical regions and withstand environmental stresses are less susceptible to supply chain disruptions, over-exploitation of wild populations, and high cultivation costs. This directly supports the long-term viability of *D. sissoo* as a raw material for pharmaceutical production, aligning with principles of sustainable development and ensuring a consistent supply.

Morphologically, *D. sissoo* is a medium to large tree, capable of reaching heights of up to 25 meters and diameters of 2 to 3 meters, though it is typically smaller. It features a light, spreading crown supported by large upper branches. The leaves are leathery, alternate, and pinnately compound, typically about 15 cm long, composed of 3-5 broadly elliptic or ovate leaflets arranged alternately on a somewhat zigzag axis. Its flowers are small, fragrant, and range from whitish to pink, appearing in dense clusters. The fruit is a distinctive thin, strap-shaped pod, 4 to 8 cm long, containing one to five flat, bean-shaped seeds. The plant possesses a long taproot system with numerous surface roots that readily produce suckers, contributing to its reproductive success. This dual reproductive strategy, involving both seeds and root suckers, offers flexibility in cultivation approaches. While seed viability is limited to a few months, root suckers provide an alternative for propagation. For industrial-scale drug production, consistent quality and quantity of raw material are paramount. Research into optimizing vegetative propagation, for instance, through the use of auxins like Indole-3-butyric acid (IBA) to enhance rooting of stem cuttings, is crucial. Such advancements would enable clonal propagation of high-yielding or specific chemotypes, thereby ensuring genetic uniformity and consistent phytochemical profiles, which are essential for pharmaceutical quality control and batch-to-batch reproducibility.

1.2. Historical and Ethnobotanical Significance

Dalbergia sissoo has been deeply interwoven with traditional medicine systems for millennia, particularly Ayurveda and Yunani, underscoring its long-standing recognition for therapeutic properties. Its traditional applications are remarkably diverse, addressing a wide spectrum of health conditions. These include metabolic disorders such as obesity and vitiligo; a variety of dermatological issues like leprosy, general skin diseases, scabies, boils, wounds, and ulcers; infectious diseases including gonorrhea, syphilis, and intestinal parasites; and inflammatory conditions characterized by fever,

pain, sciatica, hemiplegia, and broader systemic inflammations. Beyond these, it has been traditionally used for emaciation, vomiting, urinary tract disorders, and as a blood purifier.

The traditional practices often involve specific parts of the plant for distinct therapeutic purposes, indicating a nuanced understanding of its properties. For example, leaf decoctions are used in the treatment of gonorrhea and non-healing wounds, and leaf juice is applied for eye ailments. The wood and heartwood are utilized for conditions such as leprosy, fever, and for correcting lipid profiles, including lowering LDL and VLDL while increasing HDL. The bark is traditionally employed for Vata disorders like sciatica and hemiplegia, as well as for various skin conditions. Roots are specifically used for treating diarrhea and dysentery. Additionally, the twigs are commonly used for teeth brushing in many rural areas, and the plant has been noted for its pesticidal properties. . This extensive traditional knowledge serves as a robust empirical foundation for modern pharmacological investigation, providing valuable leads for targeted research. It implies that *D. sissoo* may possess a diverse array of compounds capable of multi-target therapeutic effects, a highly desirable characteristic in the development of drugs for complex diseases. The subsequent scientific validation of many of these traditional uses further strengthens its credibility as a valuable medicinal plant.

The recurring theme of using different parts of *D. sissoo* (leaves, bark, wood, roots, seeds, flowers) for distinct therapeutic purposes further supports this. This traditional specificity strongly suggests that the distribution and concentration of active phytochemicals vary significantly among different plant parts. This is a crucial consideration for medicinal chemists and drug developers, as it guides targeted extraction and isolation efforts. By focusing on the most appropriate plant part for a specific therapeutic indication, researchers can optimize extraction protocols, enhance the yield of desired compounds, and potentially improve the potency and selectivity of drug candidates.

1.3. Overview of Natural Products in Drug Discovery

Natural products, particularly those derived from higher plants, continue to be an indispensable source of new chemical entities in drug discovery. Annually, approximately two-thirds of all newly discovered chemicals across various industries, including pharmaceuticals, originate from natural sources. This enduring relevance underscores the unique chemical diversity and biological activity inherent in natural compounds, which often possess complex structures and novel mechanisms of action that are challenging to replicate through synthetic chemistry.

Plant-derived natural prescription drugs are experiencing a resurgence in global popularity. This trend is driven by a growing preference for natural-based medicines and health products, often attributed to their perceived accessibility, affordability, and the absence of synthetic ingredients. This shift reflects a broader societal movement towards holistic health and a recognition of the limitations and side effects associated with purely synthetic pharmaceuticals. The genus *Dalbergia*, to which Sheesham belongs, is particularly noteworthy in this context, as it is known to be rich in isoflavones and neoflavones, and many species within this genus have well-documented medicinal properties and traditional uses.

2. PHYTOCHEMICAL PROFILE OF *DALBERGIA SISSOO*

2.1. Major Classes of Bioactive Compounds

Dalbergia sissoo is recognized as an abundant source of a wide array of phytochemicals, which are largely responsible for its diverse pharmacological activities. Comprehensive analyses of various parts of the plant have consistently identified several primary classes of bioactive compounds. These include phenolics, alkaloids, flavonoids, saponins, phytosterols, tannins, carbohydrates, and proteins. Further detailed phytochemical investigations have revealed the presence of additional compound classes, such as glycosides, flavanols, sterols, terpenoids, quinones, benzofurans, benzophenols, stilbenes, phthalates, xanthones, and lignans.

Beyond these broad categories, specific components are found in different plant parts. For instance, the seed oil of *D. sissoo* contains significant amounts of various fatty acids, including palmitic (16.2%), stearic (7.0%), oleic (14.6%), linolenic (9.8%), and linoleic (52.5%) acids. This oil also comprises different types of lipids, specifically neutral lipids (88.5%), glycolipids (7.2%), and phospholipids (4%). Essential oils, particularly from the flowers and heartwood, have been found to contain sesquiterpene derivatives such as bisabolene and nerolidol. Quantitative analyses of *D. sissoo* extracts have provided insights into the concentration of certain key compounds. Total phenolic content has been reported to range from 50.8 mg to 58.06 mg gallic acid equivalents (GAE) per gram of extract, while tannin content varies from 61.75 mg to 218.34 mg catechin equivalents (CE) per gram of extract.

The extensive list of identified phytochemical classes directly correlates with the wide array of traditional medicinal uses and scientifically validated pharmacological activities of *D. sissoo*. Each identified class of compounds typically exhibits distinct biological properties, and their collective presence suggests that *D. sissoo* likely exerts its therapeutic effects through a complex interplay of multiple compounds acting on various biological targets and pathways. This “polypharmacology” approach is increasingly recognized as beneficial for treating multifactorial diseases, potentially offering more comprehensive efficacy and reduced chances of resistance or specific side effects compared to drugs targeting a single pathway. This makes *D. sissoo* a promising candidate for developing multi-component drug formulations or identifying lead compounds with pleiotropic effects.

2.2. Key Isolated Compounds and Their Structures

The comprehensive phytochemical investigations of *Dalbergia sissoo* have led to the isolation and characterization of numerous specific bioactive compounds from different parts of the plant. These isolated compounds provide a molecular basis for the plant’s traditional uses and observed pharmacological activities.

Among the prominent compounds identified are several isoflavones and their glycosides, including **Biochanin A** and **Tectorigenin**. Biochanin A is a 4'-methylgenistein, with the chemical formula $C_{16}H_{12}O_5$ and a canonical SMILES of COC1=CC=C(C=C1)C2=COC3=CC(=CC(=C3C2=O)O)O. Tectorigenin, a methoxyisoflavone, has the chemical formula $C_{16}H_{12}O_6$ and a SMILES of COC1=C(C2=C(C=C1O)OC=C(C2=O)C3=CC=C(C=C3)O)O. Both Biochanin A 7-O- and Tectorigenin 7-O- have been isolated as isoflavone glycosides from *D. sissoo*.

Other significant compounds include **Dalbergin** and **Dalbergichromene**. Dalbergin, a coumarin derivative, has a molecular formula of $C_{16}H_{12}O_4$ and a SMILES of COc1cc2oc(=O)cc(-c3ccccc3)c2cc1O. Dalbergichromene, a neoflavene (a type of neoflavonoid), has a chemical formula of $C_{16}H_{14}O_3$ and a SMILES of COC1=C(C=C2C(=CCOC2=C1)C3=CC=CC=C3)O. This compound is found in the stem-bark and heartwood.

A chalcone named **Okanin**, specifically (E)-3-(3,4-dihydroxyphenyl)-1-(2,3,4-trihydroxyphenyl)prop-2-en-1-one, has been isolated from the leaves, with a SMILES of Oc1ccc(/C=C/C(=O)c2ccc(O)c(O)c2O)cc1O. Other important isolated compounds include **Caviunin glucosides** (e.g., caviunin 7-O-[β-d-apiofuranosyl-(1→6)-β-d-glucopyranoside]), **Sissotrin**, **Muningin**, **Genistein**, and **Pratensein**. Additional compounds such as Irisolidone, Prunetin, Norartocarpetin, β-amyrin, β-sitosterol, Stigmasterol, Dalbergenone, and Methyl dalbergin have also been identified.

The identification of specific compounds with known chemical structures is crucial for understanding the precise mechanisms of action and for developing standardized extracts or isolated drug candidates. This advancement moves beyond the use of crude extracts to a more targeted approach in drug development, allowing for greater control over the therapeutic properties. Furthermore, understanding the chemical structures of these compounds enables detailed structure-activity relationship (SAR) studies. SAR is fundamental for rational drug design, allowing medicinal chemists to modify and optimize these natural compounds to potentially create more potent, selective, or safer analogs. This systematic approach is vital for the progression of *D. sissoo* derived compounds into modern pharmaceutical agents.

3. PHARMACOLOGICAL ACTIVITIES AND MECHANISMS OF ACTION

3.1. Anti-inflammatory and Analgesic Effects

Dalbergia sissoo has demonstrated significant anti-inflammatory and analgesic properties, validated across various experimental models. Studies have shown that ethanolic extracts of *D. sissoo* leaves and bark can significantly inhibit carrageenin, kaolin, and nystatin-induced paw edema in rats, reduce the weight of granuloma induced by cotton pellets, and decrease dye leakage in acetic acid-induced vascular permeability tests in mice. These effects were observed across acute, sub-acute, and chronic models of inflammation, and importantly, the leaf extract was found to be devoid of ulcerogenic effects on the gastric mucosa, a common side effect of many synthetic anti-inflammatory drugs.

The mechanism underlying these effects is believed to involve the plant's rich flavonoid content. Flavonoids are reported to be prostaglandin synthetase inhibitors. Since prostaglandins play a key role in pain perception and the inflammatory cascade, their inhibition by flavonoids could explain the observed anti-inflammatory and antinociceptive activities. A methanolic extract of *D. sissoo* heartwood also showed a biphasic response in carrageenan-induced paw edema, indicating involvement of both early (amine-mediated) and later (prostaglandin-mediated) phases of inflammation. The consistent anti-inflammatory and analgesic effects observed across multiple animal models and different types of pain (chemical, heat) enhance the credibility of these activities. This suggests broad applicability in the management of pain and inflammation. The attribution of these effects to specific phytochemicals like flavonoids provides a clear chemical basis for the observed activity, which is crucial for guiding further isolation, characterization, and optimization efforts in drug development.

3.2. Antidiabetic Activity

The antidiabetic potential of *Dalbergia sissoo* has been well-documented. Ethanolic extracts of *D. sissoo* leaves have been shown to significantly reduce blood glucose levels in alloxan-induced diabetic rats, with some studies reporting the extract to be 12% more effective in reducing blood glucose compared to the standard drug Glibenclamide. Beyond glucose regulation, these extracts have demonstrated the ability to restore lipid profiles, improve liver glycogen levels, normalize body weight, and enhance antioxidant status in diabetic animal models.

The antidiabetic effects are associated with the presence of polyphenols and chlorogenic acid. Recent in-silico studies, utilizing molecular docking and dynamics simulations, have provided insights into potential molecular targets. These studies suggest that compounds within *D. sissoo* extracts, such as Soyasapogenol B and Corydine, can interact favorably with key enzymes involved in glucose metabolism, including α-amylase, α-glucosidase, and Dipeptidyl Peptidase 4 (DPP-4). The inhibition of these enzymes is a recognized strategy for managing type 2 diabetes mellitus. The reported superior efficacy of *D. sissoo* extracts compared to standard medications in some preclinical models is a significant finding that warrants further in-depth investigation for the development of novel antidiabetic agents.

3.3. Anticancer Potential

Dalbergia sissoo exhibits promising anticancer potential, particularly against leukemia. Studies have demonstrated the cytotoxic potential of its leaf extracts against leukemia K562 cells, primarily through the inhibition of C-ABL kinase. Molecular docking and simulation studies have identified specific compounds, such as Biorobin, as key inhibitors with strong binding affinities to the C-ABL kinase domain. C-ABL kinase plays a vital role in regulating the actin cytoskeleton and cell cycle, and its inhibition can lead to an anticancer effect.

The proposed mechanisms of action include the inhibition of the AKT/NF-κB signaling pathway and the activation of TNF-alpha and STAT-3, which subsequently trigger signaling pathways involving the Bcl-2 family of proteins, Cyt-C, caspase 3, and caspase 9, ultimately leading to apoptosis and suppression of cell growth. The identification of specific molecular targets like C-ABL kinase and the compound Biorobin provides a clear pathway for rational drug design and the development of targeted cancer therapies. This precision moves beyond general cytotoxicity to specific molecular interactions, allowing for more focused drug development. Additionally, the presence of compounds with estrogenic activity, such as biochanin A, and general antioxidant properties suggests a potential role for *D. sissoo* in chemoprevention, particularly in hormone-sensitive cancers, by modulating cellular processes and reducing oxidative damage.

3.4. Osteogenic and Fracture Healing Properties

The osteogenic and fracture healing properties of *Dalbergia sissoo* have garnered significant attention. Preclinical studies in animal models of postmenopausal osteoporosis have shown that extracts from *D. sissoo* leaves can promote bone formation, reduce inflammation, and accelerate fracture healing. These effects are mediated by an increase in alkaline phosphatase activity and mineralization in primary calvarial osteoblast cultures, which are key indicators of bone formation.

Key compounds implicated in these effects include caviunin glucosides, particularly caviunin 7-O- (CAFG), and other methoxyisoflavones such as biochanin A and pratensein. These compounds have been shown to stimulate new bone formation and are considered potential dietary supplements for osteoporosis. A notable development is the progression of these findings from preclinical animal models to pilot clinical studies. A one-year open-labeled prospective clinical study in postmenopausal women with osteoporosis demonstrated that a standardized extract of *D. sissoo* leaves (SEL-Ds) was well-tolerated and exhibited anti-osteoporotic and anti-inflammatory activities, evidenced by reductions in TNF-α and alkaline phosphatase (ALP) levels, and maintenance of bone mineral density (BMD). Another pilot clinical study on long bone fracture healing also showed promising results, with all fractures healed by week 8 and no significant adverse events. The transition from preclinical animal models to human pilot clinical studies represents a significant step towards therapeutic application, strengthening the evidence for human benefit. This progression is vital for the 3.6. Other Pharmacological Activities

Beyond the extensively studied areas, *Dalbergia sissoo* exhibits a broad spectrum of other pharmacological activities, reinforcing its versatility as a medicinal plant. These include antimicrobial (antibacterial, antifungal), antioxidant, anti-ulcer, anti-diarrheal, anti-spermatogenic, cardioprotective, gastroprotective, anthelmintic, anti-pyretic, molluscicidal, anti-larvicidal, anti-aging, spasmolytic, aphrodisiac, and expectorant properties. It is also traditionally recognized as a blood purifier.

Specific applications include its use in treating non-specific diarrhea in animals, particularly goats, where decoctions of *D. sissoo* leaves have shown significant reduction in defecation frequency and normalization of feces. The plant's oil has demonstrated larvicidal activity against mosquitoes, and its extracts have shown anti-termite activity, indicating potential as natural pesticides. The sheer breadth of pharmacological activities observed in *D. sissoo* reinforces its status as a highly versatile medicinal plant. This wide range of effects may stem from synergistic interactions among its diverse phytochemicals, offering potential for broad-spectrum therapeutic agents that can address multiple symptoms or underlying pathologies simultaneously. Furthermore, the utility of *D. sissoo* extends beyond human medicine, with documented applications as a pesticide (anti-termite, larvicidal) and in animal health (anti-diarrheal in goats). This demonstrates broader utility, suggesting significant potential for the development of new products in agricultural and veterinary sectors, leveraging its natural properties for sustainable solutions.

4. ADVANCED USAGE IN THE DRUG INDUSTRY

4.1. Drug Formulation Advancements

The pharmaceutical industry is increasingly exploring advanced formulation strategies to enhance the therapeutic efficacy of natural product compounds, and *Dalbergia sissoo* is no exception. Recent research has focused on incorporating *D. sissoo* extracts into novel drug delivery systems, such as ethosomal gels for transdermal application. These ethosomal formulations aim to improve the penetration and bioavailability of active compounds through the skin, offering a non-invasive and potentially more effective delivery route.

Beyond ethosomal gels, the application of nanotechnology in drug delivery is revolutionizing how *D. sissoo* compounds can be utilized. Nanoformulations, including liposomes and various types of nanoparticles, offer significant advantages by improving drug solubility, enhancing bioavailability, increasing permeability across biological barriers, and improving the stability of active pharmaceutical ingredients. These nanoscale carriers can be engineered to selectively target diseased cells or tissues, thereby increasing efficacy and reducing systemic side effects, which is a critical goal in modern pharmacology. Furthermore, *D. sissoo* leaf extracts have been successfully used in the green biogenic synthesis of metallic nanoparticles, including gold, silver, magnesium oxide, and cerium oxide nanoparticles. This method offers an eco-friendly and controlled synthesis route, producing well-defined nanoparticles that can serve as novel drug carriers or have other industrial applications.

4.2. Bioavailability and Pharmacokinetic Studies

Understanding the bioavailability and pharmacokinetics of *Dalbergia sissoo* compounds is crucial for their successful development into pharmaceutical drugs. Recent studies have employed in-silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis to predict the drug-like properties and oral bioavailability of potential compounds identified in *D. sissoo* extracts. These computational approaches have revealed that several compounds adhere to Lipinski's rule of five, indicating favorable drug-like characteristics and suggesting good oral bioavailability. Molecular docking

and dynamics simulations have further demonstrated strong interactions of these compounds with specific drug targets and favorable permeability across biological membranes, such as the plasma membrane, compared to some standard drugs.

4.3. Standardization and Quality Control

The development of *Dalbergia sissoo* into reliable pharmaceutical products necessitates rigorous standardization and quality control measures. Standardization is paramount for ensuring the safety, efficacy, and consistent batch-to-batch reproducibility of herbal drugs, which is a major concern in the global herbal medicine market.

Modern analytical techniques are being employed for this purpose. High-Performance Thin-Layer Chromatography (HPTLC) and Ultra-High Performance Liquid Chromatography (UHPLC) are utilized for the simultaneous separation and quantification of bioactive marker compounds. Key marker compounds identified for standardization include caviunin 7-O- , biochanin A, pratensein, and genistein, which are osteogenic methoxyisoflavones. Metabolomic analysis, particularly using UPLC-MS/MS, provides a high-throughput chemical detection method for small-molecule metabolites, allowing for the identification and quantification of differential metabolites between various plant parts (e.g., heartwood and sapwood) and serving as a quality control tool for drug identification and purity.

In addition to chemical profiling, DNA-based molecular markers, such as intersimple sequence repeat (ISSR) and random amplified polymorphic DNA (RAPD), are employed to study genetic diversity within *D. sissoo* species. These markers are valuable for botanical identification, detecting adulteration, and ensuring the authenticity and genetic consistency of the plant material used in pharmaceutical production. However, challenges exist in DNA extraction from *D. sissoo* leaves due to the abundance of secondary metabolites that can inhibit DNA amplification, requiring optimized protocols.

The emphasis on robust standardization methods, including HPTLC, UHPLC, metabolomics, and DNA markers, is critical for ensuring the consistent quality, safety, and efficacy of *D. sissoo*-derived pharmaceutical products. This addresses a major challenge often encountered in the development of herbal medicines, where variability in raw material can lead to inconsistent therapeutic outcomes. The combination of phytochemical profiling, bioanalytical marker quantification, and genetic characterization provides a holistic approach to quality control. This multi-faceted assessment ensures both chemical consistency of the active compounds and botanical authenticity of the plant material, which are essential for meeting stringent regulatory standards in modern drug development from natural sources.

5. SAFETY PROFILE AND TOXICITY

5.1. Acute and Sub-chronic Toxicity Studies

The safety profile of *Dalbergia sissoo* extracts has been investigated through acute and sub-chronic toxicity studies in various animal models. Research indicates a generally low acute toxicity for *D. sissoo* extracts. For instance, ethanolic extracts of the bark have been found to be safe in Wistar rats up to a dose of 3000 mg/kg body weight, with no observed toxic symptoms or mortality. Similarly, ethanolic leaf extracts were reported to be safe in mice up to 10.125 g/kg orally. Furthermore, studies on leaf extracts demonstrated no ulcerogenic effect on the gastric mucosa of rats in both acute and chronic tests, which is a significant advantage over many conventional anti-inflammatory drugs.

While the plant itself has been investigated for its tolerance and accumulation of heavy metals like lead (Pb), showing high tolerance and accumulation in its roots, these studies focus on the plant's environmental role as a phytostabilizer and do not directly address the toxicity of *D. sissoo* extracts to mammals. The consistent reporting of low acute toxicity across various animal models suggests a favorable safety margin for *D. sissoo* extracts. This is a crucial initial step for pharmaceutical development, as it reduces early-stage development risks and indicates that the extracts are unlikely to cause immediate severe adverse reactions. However, while general toxicity appears low, traditional uses mention specific contraindications, such as during pregnancy, for individuals with constipation, or in cases of heavy periods. This highlights the need for a nuanced approach to safety assessment, moving beyond general acute toxicity to investigate specific adverse effects, potential drug-drug interactions, and long-term safety, which are critical for clinical application.

6. CHALLENGES AND FUTURE DIRECTIONS

6.1. Cultivation and Sustainable Sourcing

While *Dalbergia sissoo* exhibits remarkable ecological resilience, its cultivation for industrial pharmaceutical use presents specific challenges. The tree is sensitive to temperatures below 28°F (-2°C), with young and newly planted trees being particularly vulnerable to frost damage, and older trees sustaining serious damage in freezing conditions. This limits its cultivation in colder regions or necessitates protective measures. Furthermore, *D. sissoo* develops thick surface roots that can pose challenges for landscape management, potentially lifting pavements and foundations if planted too close to structures. The tree also produces a considerable amount of litter from brittle branches and falling seed pods, requiring regular cleanup.

Despite its IUCN conservation status as "Least Concern" , concerns about overharvesting exist in some regions, particularly given its high value as timber and its medicinal uses. This apparent discrepancy highlights the need for proactive and sustainable sourcing practices to prevent future depletion of wild populations and ensure a consistent supply for the drug industry. Proper site selection, favoring well-drained, sandy loam soils with adequate moisture, is crucial to avoid diseases like Fusarium Wilt and Ganoderma Root Rot, which can severely impact plantations. Optimizing vegetative propagation techniques, such as the use of IBA-treated stem cuttings, is essential for mass multiplication of planting stock, ensuring genetic uniformity, and avoiding issues like dieback disease and poor growth observed in some plantations.

The tension between the plant's high utility (for timber and medicine) and concerns about overharvesting, despite its "Least Concern" status, underscores the need for proactive conservation and sustainable cultivation strategies. This approach is vital to ensure the long-term availability of the resource for drug development and to prevent ecological degradation. Addressing cultivation challenges, such as enhancing frost resistance and managing root growth, and optimizing propagation methods are crucial for achieving consistent, high-quality biomass production. These improvements directly impact the scalability and cost-effectiveness of pharmaceutical manufacturing, making *D. sissoo* a more viable and reliable source for drug development.

6.2. Research Gaps and Opportunities

The extensive traditional uses and validated pharmacological activities of *Dalbergia sissoo* underscore its significant potential in the drug industry, yet several research gaps must be addressed to fully realize this promise. A primary need is for more rigorous clinical trials, particularly large-scale, randomized controlled trials, to definitively validate the efficacy and safety of *D. sissoo* extracts and isolated compounds across diverse patient populations and for specific indications. While pilot studies for osteoporosis and fracture healing are promising, comprehensive data on optimal dosing, long-term effects, and potential adverse reactions in humans are still limited.

Further research is also essential for isolating and characterizing more individual bioactive compounds from *D. sissoo* and elucidating their precise molecular mechanisms of action. While some pathways have been identified (e.g., C-ABL kinase inhibition in cancer, prostaglandin synthesis inhibition in inflammation), a deeper understanding of the specific targets and signaling cascades will enable rational drug design and optimization. Comprehensive pharmacokinetic and pharmacodynamic studies in vivo are critical to understand how these compounds are absorbed, distributed, metabolized, and excreted in the body, and how they interact with biological systems over time. Additionally, thorough genotoxicity and long-term toxicity studies are imperative to ensure the safety profile required for pharmaceutical products.

Opportunities for advanced usage also exist in exploring potential combination therapies with synthetic drugs to enhance efficacy or reduce side effects, and in developing innovative drug delivery systems, such as targeted nanoparticles or sustained-release formulations, to improve therapeutic outcomes.

7. CONCLUSION

Dalbergia sissoo (Sheesham tree) stands as a compelling example of a traditional medicinal plant with profound potential for advanced applications in the modern drug industry. Its rich ethnobotanical history, deeply rooted in Ayurvedic and Yunani practices, has provided a valuable empirical foundation for its therapeutic utility across a wide array of ailments, from inflammatory conditions and metabolic disorders to infectious diseases and neurodegenerative conditions. Scientific investigations have successfully validated many of these traditional uses, revealing a diverse phytochemical profile abundant in flavonoids, alkaloids, terpenoids, and phenolics, among other bioactive compounds.

The pharmacological activities of *D. sissoo* are remarkably broad-spectrum, encompassing significant anti-inflammatory, analgesic, antidiabetic, anticancer, osteogenic, and neuroprotective effects. Crucially, research has begun to unravel the underlying molecular mechanisms, identifying specific targets and pathways such as prostaglandin synthetase inhibition, C-ABL kinase inhibition, and modulation of α-amylase, α-glucosidase, and DPP-4 enzymes. This mechanistic understanding is vital for rational drug design and development.

Advancements in drug formulation, including ethosomal gels and green-synthesized nanoparticles, are poised to enhance the bioavailability, targeted delivery, and overall therapeutic efficacy of *D. sissoo* compounds. While preliminary safety studies indicate a favorable acute toxicity profile, a critical need remains for comprehensive pharmacokinetic, pharmacodynamic, genotoxicity, and long-term clinical trials to fully establish its safety and efficacy for widespread pharmaceutical application.

To realize the full potential of *Dalbergia sissoo* as a source of novel therapeutic agents, future efforts must prioritize rigorous scientific investigation, particularly in human clinical trials, and invest in robust standardization protocols using advanced analytical techniques. Concurrently, implementing sustainable cultivation and sourcing practices is paramount to ensure the long-term availability and quality of this invaluable natural resource, balancing its economic and medicinal utility with ecological stewardship. By bridging the gaps between traditional wisdom and modern scientific rigor, *Dalbergia sissoo* is well-positioned to contribute significantly to the development of new, effective, and sustainable pharmaceutical solutions.

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