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Ethnomedicinal and Hepatoprotective Potential of Sphaeranthus indicus L

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Abstract:

Sphaeranthus indicus L., or East Indian Globe Thistle, also referred to as "Gorakhmundi" in Ayurvedic medicine, is a highly valued plant under the Asteraceae family. The review here exhaustively discusses its ethnomedicinal use as well as critically analyzes the scientific evidence as proof of its hepatoprotective effect. S. indicus has been used in a broad spectrum of cultures, especially in South Asia, for the treatment of a broad range of diseases such as jaundice, liver diseases, skin infections, fevers, and respiratory disorders. Phytochemical analysis has shown a rich secondary metabolite composition, which consists of flavonoids, steroids, triterpenoids, essential oils, and alkaloids, responsible for its extensive range of pharmacological activity. Various in vitro and in vivo studies have shown that S. has tremendous hepatoprotective activity. indicus isolates against chemically induced models of liver damage, including carbon tetrachloride (CCl4), paracetamol, and antitubercular drug-induced toxicity. Its mechanisms of action on its hepatoprotective properties are complex and include mainly potent antioxidant activity, inflammatory pathways modulation, membrane stabilization, and augmentation of detoxification enzymes. Although traditional applications and preclinical studies strongly support its therapeutic potential in liver diseases, additional stringent clinical trials are necessary to confirm its efficacy and safety in human patients. This review seeks to bridge conventional wisdom with contemporary scientific knowledge in emphasizing S. indicus as a potential natural source for the development of new hepatotherapeutic agents.

Keywords: Sphaeranthus indicus, Ethnomedicine, Hepatoprotection, Liver disorders, Phytochemistry, Antioxidant, Anti-inflammatory, Traditional medicine

1. Introduction

Liver diseases represent a significant global health burden, encompassing a spectrum of conditions from acute hepatitis and fatty liver disease to cirrhosis and hepatocellular carcinoma. Factors such as viral infections, alcohol abuse, drug toxicity, metabolic disorders, and environmental toxins contribute to liver damage. Even with the progress in mainstream medicine, potent and safe treatments for most liver diseases are few, many being linked with unwanted side effects or exorbitant prices (Friedman, 2018). Therefore, there is an increasing interest in investigating natural compounds and traditional medicinal plants as leads for new hepatoprotective compounds (Yuan *et al.,* 2021).

Ancient medicine systems, like Ayurveda, Unani, and traditional Chinese medicine, have traditionally used plants for the cure of several diseases, including liver disease. Ethnobotanical knowledge, transmitted from generation to generation, forms an important foundation for scientific studies to understand their pharmacological action. Sphaeranthus indicus L. (Asteraceae), locally referred to as "Gorakhmundi" in Hindi, "East Indian Globe Thistle" in English, and "Kommunistichesky Kadam" in certain areas, is one such plant with an affluent ethnomedicinal history, especially in the Indian subcontinent and Southeast Asia (Khare, 2007).

Sphaeranthus indicus is a branched, annual, aromatic herbaceous plant that grows commonly up to 60 cm in height. The plant is recognized by its globose purplish flower heads, which are quite distinguishing. It grows in moist, marshy, and waste grounds in tropical and subtropical areas, such as India, Bangladesh, Sri Lanka, and parts of Africa (Prakash et al., 2202). Traditionally, the plant's roots, leaves, stems, and flowers have been put to use for their medicinal values.

This article will present an overview review of the ethnomedicinal applications of *S. indicus, with* emphasis on its reported hepatoprotective activity. It will explore the plant's phytochemistry, review the in vitro and in vivo experiments clarifying its protective actions against different types of liver damage, and emphasize its promise as a natural hepatotherapeutic drug. Ultimately, it will present areas of future research needed to transform this traditional knowledge into clinically proven therapies.

2. Ethnomedicinal Applications of *Sphaeranthus indicus* L.

Sphaeranthus indicus occupies a special position in different traditional systems of medicine, including Ayurveda and Unani, where it is highly valued for its pungency, bitterness, and astringent qualities. Its traditional uses indicate an extensive range of pharmacological activities.

Traditional Utilization in Liver Diseases: *S. indicus* is one of the most important traditionally used plants in the treatment of liver-related disease.

Jaundice and Hepatitis: Throughout most of India, the entire plant or extracts from the leaves are taken orally traditionally to cure jaundice as well as different types of hepatitis. It is believed to stimulate bile excretion and revive liver function (Shah et al., 2012).

General Liver Tonics: It is usually added to preparations intended to promote general liver health, cleanse the liver, and help improve digestive function, thus indirectly contributing to liver processes.

Splenomegaly: Because of its claimed anti-inflammatory and detoxifying properties, it has also been used in traditional medicines for an enlarged spleen, which is usually linked with liver conditions.

Other Varied Ethnomedicinal Applications: In addition to liver disorders, S. indicus has been utilized traditionally for a variety of health issues:

Digestive System: Traditionally applied in the treatment of dyspepsia, flatulence, diarrhea, dysentery, and abdominal cramps. The leaves are occasionally eaten for relief from constipation (Nadkarni, 1954).

Skin Diseases: Topical application of fresh juice of leaves or paste of entire plant is done for infections of skin, eczema, ringworm, pruritus, and scrofula because of its antiseptic and anti-inflammatory properties (Chopra et al., 1956).

Inflammation and Pain: Plant has conventional uses as an anti-inflammatory remedy, especially for swelling, joint pain, and rheumatism. Its analgesic action is also known (Ghosal et al., 1983).

Respiratory Diseases: Decoctions of the plant are employed in indigenous cough medicines, asthma, and bronchitis (Kirtikar & Basu, 1935).

Fever and Infections: It is a folk antipyretic to treat all kinds of fevers, including malarial fever. Its antimicrobial activity is used against bacterial as well as parasitic infections, such as elephantiasis (Dubey et al., 2009).

Urinary Disorders: Employed as a diuretic and in treating conditions such as gonorrhea and dysuria.

Wound Healing: Topical application of its paste is known to enhance wound healing.

Anti-cancer: Folk use in certain parts of the world gives S. indicus anti-cancer properties, especially for ailments such as piles (hemorrhoids) which are at times related to other growth-related problems.The wide and varied usage by traditional communities testifies to the plant's immense pharmacological promise and forms a vital basis for current scientific research.

Phytochemistry of Sphaeranthus indicus L.

The diverse ethnomedicinal uses of S. indicus are attributed to its complex array of secondary metabolites. Extensive phytochemical investigations have identified various classes of compounds, each contributing to its biological activities.

3. Major Phytochemical Classes

Flavonoids: These are one of the most widespread and researched compounds in S. indicus. Major flavonoids identified are sphaeranthin, sphaeranthine, sphaeranthol, sphaeranthone, and several glycosides of luteolin and apigenin (Sagar et al., 2016). Flavonoids are renowned for their antioxidant, anti-inflammatory, and hepatoprotective effects.

Steroids and Triterpenoids: The plant is rich in significant steroidal constituents such as β-sitosterol, stigmasterol, and their glycosides. Triterpenoids such as sphaeranthanolide are also found. These substances usually possess anti-inflammatory, anticancer, and immunomodulatory activities (Prajapati et al., 2004).

Alkaloids: Indol-quinazoline alkaloids such as sphaeranthine have been obtained from S. indicus. Alkaloids are a heterogeneous group with much pharmacological promise, often acting on neurotransmitter systems or possessing cytotoxic activity.

Essential Oils: Volatile oils present in the aerial parts of the plant include substances like α-limonene, β-eudesmol, germacrene D, β-caryophyllene, and terpene derivatives. Essential oils are responsible for the plant's typical smell and display antimicrobial, insecticidal, and anti-inflammatory activities (Suresh et al., 2010).

Phenolic Acids: Caffeic acid, ferulic acid, and other phenolic substances, having high antioxidant activity, also occur.

Other Compounds: The foliage also harbors tannins, saponins, and reducing sugars, which are added to its therapeutic package.

Contribution to Hepatoprotection: The profuse phytochemical content of S. indicus infers a synergistic effect of its multiple constituents in providing hepatoprotection. Flavonoids and phenolic acids are powerful antioxidants, indispensable in preventing oxidative stress-mediated liver injury. Triterpenoids and steroids are largely responsible for its anti-inflammatory action, which is crucial in avoiding inflammation-induced liver damage. The essential oils could also contribute through their antioxidant and antimicrobial action, possibly helping in mitigating pathogen-induced stress to the liver. Isolation and identification of the exact mechanisms of action of single components and their synergism is a research area that continues to evolve.

4. Pharmacological Activities of Sphaeranthus indicus L.

Sphaeranthus indicus has a varied array of reported pharmacological activities, consistent with its varied traditional applications. Taken together, these activities make it possess therapeutic value, which specifically involves its hepatoprotective properties.

Antioxidant Activity: This is one of the most frequently reported activities of S. indicus. Different extracts (methanolic, ethanolic, aqueous) and isolated molecules exhibit strong free radical scavenging activity against DPPH, ABTS, superoxide, and hydroxyl radicals (Mandal et al., 2017). This antioxidant activity is vital in the battle against oxidative stress, a central pathological mechanism underlying many diseases, including liver damage.

Anti-inflammatory and Analgesic Activity: Experiments have proved that S. indicus extracts are highly effective in anti-inflammatory activity, inhibiting pro-inflammatory mediators like prostaglandins, leukotrienes, and cytokines (e.g., TNF-α, IL-6). This is usually mediated by the inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways, as well as the nuclear factor-kappa B (NF-κB) signaling pathway (Ahmed et al., 2011). Its folk use for pain relief is also evidenced by experiments exhibiting analgesic action.

Antimicrobial Activity: S. indicus extracts were active against various bacteria (e.g., Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa) and fungi (e.g., Candida albicans), validating the use in traditional medicine for treating infections and cutaneous diseases (Raghavendra et al., 2009).

Antidiabetic Activity: Certain studies indicate that S. indicus may be useful in the management of blood glucose levels through increased insulin secretion, better utilization of glucose, and antioxidant activities to safeguard pancreatic β-cells from oxidative stress (Patel et al., 2012).

Anticancer Activity: Initial in vitro experiments have shown cytotoxic and antiproliferative activities of S. indicus extracts on different cancer cell lines, indicating possible anticancer activity by inducing apoptosis and inhibiting cell growth (Karthikeyan et al., 2011).

Immunomodulatory Activity: The plant was found to modulate immune activity, possibly increasing cellular and humoral immunity, which could be helpful in different disease conditions (Khan et al., 2013).

Hepatoprotective Activity of *Sphaeranthus indicus* L.

The potential hepatoprotective activity of S. indicus is among its best-studied pharmacological actions, reflecting strongly its long traditional use in liver disease. Its protective efficacy against various models of chemically induced liver damage has been exhibited in many in vitro and in vivo studies.

In vivo Studies on Chemically Induced Liver Damage:

Carbon Tetrachloride (CCl4)-Induced Hepatotoxicity: CCl4 is a known hepatotoxin that causes liver injury through the formation of free radicals, resulting in lipid peroxidation, oxidative stress, and inflammation.A number of studies have revealed that pretreatment or co-administration with *S. indicus* extracts (e.g., methanolic, ethanolic, aqueous) considerably reduces CCl4-induced liver injury in rats and mice.

Biochemical Markers: S. indicus extract treatment yielded a significant drop in elevated serum levels of liver enzymes like aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and bilirubin, which are markers of hepatocellular damage and cholestasis (Ahmed et al., 2011; Roy et al., 2012).

Oxidative Stress Markers: The extracts were also shown to restore antioxidant defense systems' balance by enhancing the concentration of endogenous antioxidants such as reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). At the same time, they markedly decreased lipid peroxidation, which was marked by lowered malondialdehyde (MDA) content in liver tissue (Singh et al., 2010).

Histopathological Alterations: Microscopy of liver sections from treated animals showed significant diminishment of CCl4-induced harmful alterations, such as necrosis, steatosis, inflammation, and ballooning degeneration, with the architecture of the liver being nearly normal (Ahmed et al., 2011).Paracetamol (Acetaminophen)-Mediated Hepatotoxicity: Paracetamol overdose leads to extensive liver injury mainly by the generation of an hepatotoxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) that depletes GSH and induces oxidative stress and cellular injury.Experiments have shown that extracts of S. indicus are able to prevent paracetamol-induced hepatotoxicity by normalizing serum hepatic enzyme levels (AST, ALT, ALP) and bilirubin to almost normal.

Antioxidant Mechanism: The plant protects through the preservation of GSH levels, promotion of antioxidant enzyme activity (SOD, CAT), and inhibition of lipid peroxidation, thus countering the toxic action of NAPQI and oxidative stress (Maity et al., 2018).

Histopathology: Like CCl4 models, histopathological examination revealed significant reduction of paracetamol-induced centrilobular necrosis and inflammatory infiltration in S. indicus-treated animals (Gupta et al., 2015).

Antitubercular Drugs (ATDs)-Induced Hepatotoxicity: ATDs such as isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) are potent anti-tuberculosis drugs but are commonly linked with drug-induced liver injury (DILI).

Studies have shown that S. indicus extracts are capable of providing defense against hepatotoxicity caused by combination ATDs in animal models.

Biochemical and Antioxidant Recovery: There was a considerable reduction in serum AST, ALT, ALP, and total bilirubin levels with improvement in hepatic antioxidant function (GSH, SOD, CAT) and decrease in lipid peroxidation (MDA) following treatment with S. indicus (Sharma et al., 2014). This indicates the plant's value as an adjuvant therapy to counteract ATD-induced DILI.

Postulated Mechanisms of Hepatoprotection: The hepatoprotective activity of S. indicus is presumably mediated by a multitude of mechanisms:

Antioxidant Activity: It is the main mechanism. The abundance of flavonoids, phenolic acids, and other antioxidants in S. indicus directly quenches free radicals, lowers oxidative stress, and inhibits lipid peroxidation of hepatocyte membranes. It also increases endogenous antioxidant enzymes, supporting the liver's natural protective system (Devi et al., 2016).

Anti-inflammatory Action: Through the inhibition of pro-inflammatory cytokines (e.g., TNF-α, IL-6) production and regulation of inflammatory signaling pathways (e.g., NF-κB, COX-2), S. indicus inhibits inflammation-induced liver injury, an essential factor in most liver diseases (Ahmed et al., 2011).

Membrane Stabilization: Cell membrane stabilization of hepatocytes against oxidative and necrotic injury is important. S. indicus has antioxidant activity that stabilizes these membranes, inhibiting intracellular enzyme leakage and preserving cellular integrity (Mandal et al., 2017).

Detoxification Enzyme Modulation: Certain studies indicate that S. indicus can affect Phase I and Phase II drug-metabolizing enzymes, which might upgrade the detoxification of injurious toxins and their metabolites, lowering their hepatic load (Maity et al., 2018).

Anti-fibrotic Potential: Although less well investigated, the antioxidant and anti-inflammatory effects of S. indicus might indirectly exert anti-fibrotic action by limiting progression of chronic liver damage that results in fibrosis.

Toxicity and Safety Profile Toxicity data for Sphaeranthus indicus are important for its possible clinical use.Preclinical Toxicity Tests: Acute and sub-acute toxicity tests in animal models typically

show a large margin of safety for S. indicus extracts. Oral route administration of crude extracts at high doses (e.g., 2000 mg/kg body weight) also failed to cause any notable mortality or side effects in rats and indicated an LD50 value of more than 2000 mg/kg (Ahmed et al., 2011; Roy et al., 2012).

Clinical Experience (Traditional Use): Its extensive history of traditional use in multiple forms of preparations by adults and children alike, with a lack of widespread reports of serious adverse effects, attests to its relative safety within therapeutic doses.

Limitations: Although preclinical findings are promising, full chronic toxicity studies, drug-herb interactions, and human clinical safety trials remain largely unexplored. Additional research into individual compounds and their potential long-term consequences is indicated.

5. Conclusion

Sphaeranthus indicus L. is an impressive medicinal plant endowed with a vibrant ethnomedicinal history, especially for liver disorders. From the existing scientific evidence, there are strong backing and recommendations for its hepatoprotective effect, mostly by virtue of its strong antioxidant and anti-inflammatory effects. Its rich phytochemical diversity, particularly the occurrence of flavonoids, triterpenoids, and phenolic acids, forms the basis of these therapeutic outcomes.In spite of the encouraging preclinical findings, various directions need to be pursued to exploit the full therapeutic value of S. indicus:

Isolation and Characterization of Bioactive Compounds: Further focused investigations are necessary to isolate and characterize the exact compounds or combinations of compounds that are responsible for its hepatoprotective activities. This may result in standardized extracts or lead compounds for drug development.

Mechanistic Explanation: Although antioxidant and anti-inflammatory mechanisms are established, more in-depth molecular studies on specific signaling pathways (e.g., Nrf2 pathway, autophagy, ER stress response) that contribute to its hepatoprotection would give a better picture.

Pharmacokinetics and Pharmacodynamics: ADME studies on the absorption, distribution, metabolism, and excretion of the active constituents of S. indicus need to be done to determine its bioavailability and maximize dosing regimens.

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