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Emerging Trends in Phytomedicinal Research

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Dr. Rajesh A. Maheshwari
Dr. Dhanya B. Sen
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PREFACE

The quest for therapeutic agents from nature has been an enduring endeavor of humanity. Plants have served as a primary source of medicine since ancient times, and modern science continues to validate and expand upon traditional knowledge through advanced research. With increasing global interest in natural and holistic health remedies, phytomedicine has emerged as a significant field bridging ethnopharmacology, phytochemistry, pharmacology, and biotechnology.

This book, "Emerging Trends in Phytomedicinal Research", is a curated compilation of contemporary studies and innovative approaches in the realm of plant-based medicine. It brings together the latest findings, methodologies, and applications that underscore the dynamic evolution of phytomedicinal research. The chapters reflect a multidisciplinary approach, covering a broad spectrum of topics such as medicinal plant identification, bioactive compound isolation, mechanism of action studies, pharmacological evaluations, clinical relevance, and biotechnological advancements.

The objective of this volume is to serve as a comprehensive resource for researchers, academicians, students, and professionals working in the fields of botany, pharmacognosy, pharmacology, herbal medicine, and allied sciences. It provides a platform for knowledge exchange and fosters a deeper understanding of the therapeutic potential of phytochemicals in addressing current and emerging health challenges.

We extend our sincere gratitude to the contributing authors whose scholarly works have enriched this compilation. Their commitment to scientific excellence and passion for natural product research have made this volume possible. We also thank the editorial and publishing teams for their dedicated support throughout the publication process.

We hope this book will inspire future research, encourage collaboration, and contribute meaningfully to the advancement of phytomedicine for the betterment of global health.

- Editors

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EXPLORING THE PHARMACOLOGICAL SPECTRUM OF PUNARNAVA: FROM TRADITIONAL USES TO MODERN THERAPEUTICS

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Abstract:

Boerhavia diffusa, a medicative plant extensively used in traditional systems like Ayurveda, folk medicine as "Punarnava". Its pharmacological effects are significantly contributed due to its bioactive substances -phenolics, steroids, lignans, alkaloids (punarnavine), flavonoids, and rotenoids (boeravinones). Its important properties, including as anti-inflammatory, analgesic, hepatoprotective, diuretic, antidiabetic, anticancer, immunomodulatory, antimicrobial, antioxidant, renoprotective, cardioprotective, and antifertility effects, have been validated by scientific research. The plant has long been used to treat fever, jaundice, respiratory conditions, liver and kidney problems, and blood purification. Its strong antioxidant qualities are essential for regulating metabolic disorders and safeguarding critical organs. In support of *Boerhavia diffusa*'s ethnomedical applications and emphasizing its potential as a source for creating innovative phytopharmaceuticals for a range of medical ailments, this chapter compiles the advancement in research on the plant's phytochemistry, pharmacology, and clinical potential.

Keywords: *Boerhavia diffusa*, Liver Disorder, Punarnava, Hepatoprotective

Introduction:

Boerhaavia diffusa Linn. Family Nyctaginaceae usually called as 'Punarnava' in Asia country. This ancient herb, also known as creeping weed, has been used to cure liver problems, jaundice, and cancer.

Figure 1: *B. diffusa* plant

Diabetes, jaundice, and heart failure are treated using the roots and entire plant in many Asian countries.[1] South American nation, Africa, Australia, south Asia and the United States are among the tropic and subtropical regions where the plant is abundantly found. *B. diffusa* has a

higher nutritive value and is used as a green vegetable in India.[2] While the whole flora is used to cure a number of conditions, the roots and leaves of *B. diffusa* are often employed in traditional medicine to relieve a number of ailments.[3] Figure 1 represents the *B. diffusa* plant.

Scientific/taxonomical classification:	**Other names:**
Kingdom: Plantae	Sanskrit: Punarnava, rakta punarnava
Order: Caryophyllales	Gujarati: Dholisaturdi
Family: Nyctaginaceae	Hindi: Gadapurna, sant
Genus: Boerhavia	Marathi: Raktavasu, tambadivasu
Species: *B. diffusa*	Bengali: Rakta punarnava
Part used: Roots	Telgu: Atikamamidi

Chemical constituents

The plant has chemical components, including as lignins, alkaloids, steroids, saccharide, triterpenoids, lipids, flavonoids, proteins, and glycoproteins. The main constituents are α- & β-sitosterol, ester of β-sitosterol, ursolic acid, lirodendrin, palmitic, arachidic, stearic acid, hexacosonoic, tetracosanoic, β-Ecdysone, triacontanol, hentriacontane, and other compounds. While the herb has fifteen amino acids and six necessary amino acids, the root contains fourteen amino acids and seven essential amino acids.[4]

Pharmacological activity

Traditional use of the plant

According to Ayurveda, *B. diffusa* is classified as a "rasayana" plant, boosts vitality and mental capacity, wards off illness, slows down the aging process, and restores youth. This plant provides immunomodulation and hepatoprotection, which strengthens the body's defenses against any assault. Additionally, the B. diffusa plant is used to treat abdominal malignancies. In many ayurvedic recipes, it is an important natural element. Gynecological disorders, anemia, asthma, rheumatism, inflammation, jaundice, and ascites are among the ailments for which it has been utilized in various formulations.[5]

Sothaghna Lepa, Sukumar Ghrit, Punarnava Guggula, Punarnavambu, Punarnavasataka, Purnarnavadi Mandura, Punarnavasak Kwath/Churna, Punarnavasava are some of the traditional formulations that use *B. diffusa* as a primary ingredient. The plant is available in various forms, including capsules, tablets, powders, and extracts e.g Punarnava capsules containing pure Boerhavia diffusa extract are marketed for their health benefits.

Anti-diabetic activity

According to Pari *et al.* (2004), in rats with diabetes caused by alloxan, leaf extract significantly increased plasma insulin levels while lowering blood glucose levels and glycosylated hemoglobin levels. The extract either decreased gastrointestinal glucose absorption, increased pancreatic insulin secretion, or transported blood glucose to peripheral tissues.[6]

Antibacterial activity

Umamaheswari and coworkers (2010) studied the ethanolic extract of *B. diffusa* leaves, and proved that it kill bacteria.[7] The extract's antimicrobial efficacy against bacterial pathogens

that cause UTIs was investigated by Sahu and colleagues, (2013).[8] In clinical trials including 50 recently diagnosed patients with pulmonary tuberculosis, Kant *et al.* discovered that the extract was more advantageous for the patients in the control group when used as an adjuvant to chemotherapy. At the end of the 4-6 week follow-up period, the extract-treated patient had better recovery from fever and cough than the control group. [9]

Hepatoprotective activity

B. diffusa exhibits significant protective effects for liver against damage caused by thioacetamide, aligning with proposed mechanisms of thioacetamide-induced hepatotoxicity. [10] In rats with CCl4-induced hepatotoxicity, the plant extract significantly decreased serum bilirubin levels and decreased prothrombin time, which was elevated by CCl_4. This suggests that the drug is effective in maintaining the liver's normal functional status and can shield the liver's prothrombin synthetic activity. [11]

Immunomodulatory activity

In was previously investigated the immunomodulation by oral administration of aqueous extract at 50–200 mg/kg/day in abdominal sepsis of using an E. coli-induced model. Evidential leucocytosis and a 50% decrease in mortality in pretreated mice. At 25–100 mg/kg p.o., the extract's alkaloidal component converted to its active form, which considerably decreased and postponed the rats' hypersensitive reactions. The plant contains syringaresinol mono-D-glucoside, punarnavine, and quercetin, compounds noted for their immunomodulatory properties [12, 13]

Anticancer activity

Ahmed-Belkacem and colleagues isolated two rotenoids from *B. diffusa* roots, boeravinones G and H, and found that they might function as efflux inhibitors for the protein known to promote breast cancer resistance (ABCG2).[14] Sreeja and associates tested the methanolic extract of the entire plant's antiproliferative and antiestrogenic qualities in the MCF-7 cell line, showing a 46.8% reduction in cell viability at 320 μg/mL in 48 hours.[15] Leyon *et al.* (2005) studied the anti-metastatic effects of *Boerhavia diffusa* extract on mice, finding it enhanced NK cell activation, complement-mediated cytotoxicity, and antibody-dependent cellular cytotoxicity.[16]

Punarnavine enhanced the production of IL-2 and IFN-γ, while significantly decreasing levels of GM-CSF and proinflammatory cytokines (IL-1α, IL-6, and TNF-α). Additionally, it suppressed VEGF, ERK-1&2, MMP-2 & 9 synthesis.[17]. It has radioprotective, anticancer, and immunomodulatory qualities. An aqueous extract of *B. diffusa* has shown hepatoprotective and anti-cancer action in a model of DEN-induced carcinogenesis. B. *diffusa* has the potential to considerably improve lipid profiles, hepatic, and renal functions by reducing the effects of DEN. Furthermore, a macroscopic and histological analysis suggested that the extract may lessen the carcinogenic effects of DEN.[18] Medicinal activities of *B. diffusa* are summarized in Table 1.

Table 1: Key medicinal activities of *B. diffusa*

Pharmacological Activity	Plant Part(s) Used	Description Key Outcomes / Effects	References
Anti-inflammatory	Whole plant, leaves	Reduced edema in early and late phases of inflammation; modulation of inflammatory mediators	19, 20
Antioxidant	Leaves, roots	Enhanced enzymatic antioxidant activities (SOD, catalase, peroxidase); scavenging of free radicals	19, 20
Hepatoprotective	Roots, whole plant	Protection against liver damage; normalization of liver enzymes and improved liver function	21
Anticancer / Cytotoxic	Aerial parts, roots	Cytotoxic effects on cancer cell lines (HeLa, MCF-7); inhibition of tumor growth	21
Antidiabetic	Roots, leaves	Blood glucose lowering; improved insulin sensitivity; antioxidant support in diabetic models	21
Antimicrobial	Roots, leaves, stem	Activity against bacteria (*S. aureus*, *S. typhi*), antifungal and antiplasmodial effects	21
Renoprotective	Roots, whole plant	Protection of kidney function; normalization of serum urea, creatinine, and other renal markers	22
Cardioprotective	Whole plant	Improvement in cardiac function and protection against oxidative stress-induced cardiac damage	22
Diuretic	Roots, leaves	Increased urine output aiding in fluid balance and treatment of edema and ascites	21
Antifertility	Flowers, seeds	Contraceptive effects demonstrated in animal studies	21
Wound and Ulcer Healing	Leaves, whole plant	Promotion of wound closure and gastric ulcer healing	22

Formulation containing *B. diffusa*

Livogrit is a polyhedral formulation traditionally and scientifically employed for managing liver disorders. In screening studies, a 14-day treatment with Livogrit at an effective dose (ED_3–142 μg/kg) improved atypical serum biochemical parameters. It content has extract of Punarnava, Bhumi Amla and Makoy. Compared to prednisone, the formulation effectively reduced the liver dysfunction index to a low-risk level. Liver cytology further revealed reduced hepatocyte cell death, supporting the notable therapeutic potential of Livogrit.[23]

Nanoparticle and Mouthwash Preparations

The *B. diffusa* root extract was incorporated in nanoparticles, selenium-based, which was delivered as mouthwash for antimicrobial applications. The selenium-bound mouthwash demonstrated lower cytotoxicity compared to commercially available and had shown antibacterial activity against *Candida albicans* and *Streptococcus mutans*.[24,25]

***In-Situ* Gel Formulations:**

B. diffusa root extracts have been formulated into *In-Situ* gels, particularly for ocular drug delivery (e.g., cataract therapy).[26]

Amorphous solid dispersion

The amorphous solid dispersion (ASD) of *B. diffusa* (Linn.) root extract significantly enhanced the solubility of its phytoconstituents at drug-to-polymer ratios of 1:2 and 1:4, compared to the unprocessed extract. PVP K-30 and HPMCAS-L showed the most effective performance, achieving over 90% release of phytoconstituents within three hours. [27]

Analysis

HPTLC is widely employed to identify key markers such as boeravinone derivatives, typically using a solvent system composed of toluene, ethyl acetate, formic acid, and methanol. [28] Additionally, compounds like boeravinone B and punarnavine have been quantified using (HPLC on a C_{18} column, with methanol:water and acetonitrile as the mobile phases. [29] Gas Chromatography-Mass Spectrometry (GC-MS) analysis has identified constituents such as stigmasterol, sitosterol, phytol, and phthalic acid, while LC-MS/HRMS analysis further confirms the presence of several bioactive compounds.[30,31]

Conclusion:

B. diffusa is a versatile medicinal plant extensively used in traditional medicine systems for its wide range of therapeutic properties. Numerous pharmacological actions, including as anti-inflammatory, analgesic, hepatoprotective, renoprotective, antidiabetic, antibacterial, anticancer, antioxidant, cardioprotective, and antifertility effects, have been demonstrated in scientific investigations that have confirmed its ethnomedicinal usage. Its extensive phytochemical composition, which includes phenolics, steroids, lignans, alkaloids (punarnavine), flavonoids, and rotenoids (boeravinones), is mostly responsible for these benefits. The plant's strong antioxidant properties are essential for regulating metabolic disorders and safeguarding critical organs. All things considered, Boerhavia diffusa is a potential natural treatment with a variety of pharmacological properties that merit more research in order to generate standardized phytopharmaceuticals that can treat a range of medical ailments.

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UNLOCKING THE NUTRACEUTICAL POTENTIAL OF CHIA SEEDS: A REVIEW OF BIOACTIVE COMPOUNDS AND FUNCTIONAL PROPERTIES

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Abstract:

Salvia hispanica L., commonly known as chia, has gained widespread attention as a functional food due to its dense nutritional profile and diverse therapeutic potential. Native to Central America and historically valued by Aztec and Mayan civilizations, chia seeds are rich in omega-3 fatty acids (particularly alpha-linolenic acid), protein, dietary fiber, antioxidants, and essential minerals. This chapter reviews the phytochemical constituents and the emerging therapeutic applications of chia seeds, including their roles in preventing kidney stones, managing hypertension, modulating glycemic responses, and combating obesity. Furthermore, chia demonstrates significant antioxidant and immunomodulatory activities and is a sustainable alternative to marine-derived omega-3 sources. Regulatory endorsements and advances in oil extraction techniques underscore its growing relevance in health-oriented food systems. The findings support the inclusion of chia in dietary interventions targeting metabolic disorders and chronic disease prevention.

Keywords: *Salvia hispanica*, Chia Seed, Functional Food, Antioxidants, Dietary Fiber, Hypertension, Glycemic Control, Obesity

Introduction:

In recent years, the incorporation of seeds such as *Salvia hispanica L*. (chia seeds) into regular diets has significantly increased due to their recognized nutritional and health-promoting properties. Native to Central America, particularly Mexico and Guatemala, chia seeds were historically consumed by ancient civilizations like the Aztecs and Mayans as a staple food and in traditional medicine for over 5,000 years.[1,2] Nutritionally, chia seeds are rich in bioactive compounds and essential nutrients. They contain 20–34% lipids, with a high proportion of polyunsaturated fatty acids (PUFAs), particularly α-linolenic acid (ALA, ~60%) and linoleic acid (~20%).[3] Protein content ranges from 16% to 26%, primarily composed of prolamins, and dietary fiber comprises 23% to 41% of seed mass.[4] Chia also contains essential vitamins from the B-complex group and minerals such as calcium, phosphorus, and potassium.[5] Due to the absence of gluten, chia seeds are suitable for individuals with celiac disease.[6] Moreover, chia

seeds exhibit a broad range of functional properties. Their phytochemical profile includes antioxidants like chlorogenic acid, caffeic acid, quercetin, and kaempferol, which contribute to their anti-inflammatory, antidiabetic, and cardioprotective effects.[7,8] Multiple studies have reported that chia seed consumption leads to reductions in blood pressure, improvements in lipid profiles, and better glycemic control.[9–11] Given these benefits, chia seeds have been approved as a novel food by the European Parliament under Regulation (EC) No. 258/97 in 2013, followed by further authorizations by the European Food Safety Authority (EFSA) for inclusion in various food categories.[12–14] In the United States, they are recognized as a dietary ingredient in the USDA National Nutrient Database.[15] These regulatory approvals highlight chia's rising importance in the health food sector. The seeds' gel-forming ability, due to their high polysaccharide content, allows their use in thickening, stabilizing, and emulsifying food systems, increasing their applicability in the food industry.[16] Chia can be consumed whole, ground, processed into oil, or used as flour in food formulations.

Phytochemical constituents

Chia seeds (*Salvia hispanica L.*), members of the Lamiaceae (mint) family, are recognized for their rich nutritional composition and diverse phytochemical constituents. The seeds are small, oval-shaped, and typically gray with a mottled pattern of black and white, measuring approximately 2 mm in diameter.[17] While both black and white chia seeds are cultivated, the black variety is more prevalent due to higher yield efficiency. White seeds, being slightly larger, are selectively propagated to ensure uniformity through pre- and post-harvest sorting. [18] Nutritionally, chia seeds are a substantial source of macronutrients including plant-based proteins (approximately 16–26%), lipids (20–34%), carbohydrates, and dietary fiber, with fiber alone accounting for nearly 40% of the seed's dry weight. [19, 20] This significant fiber content includes both insoluble and soluble fractions, each contributing distinct physiological benefits. Insoluble fiber, primarily cellulose, remains undigested as it passes through the gastrointestinal tract. Its presence in the diet is known to increase fecal bulk, promote intestinal motility, and alleviate constipation. Additionally, insoluble fiber assists in the excretion of cholesterol and potentially carcinogenic substances, thereby supporting overall gut and metabolic health.[21,22] Chia seeds are among the most fiber-dense foods, with their high fiber content playing a key role in their gel-forming capacity upon hydration—an attribute that facilitates fecal regularity and bowel health.[23]

Soluble fiber, on the other hand, dissolves in water to form a viscous gel, contributing to enhanced fecal bulk and moisture. This fiber type slows gastric emptying, stabilizes postprandial glucose responses, and prolongs satiety, making it beneficial for glycemic control, cholesterol reduction, and weight management.[24,25] Soluble fiber in chia is also associated with colon health and may possess anti-aging effects due to its antioxidant interactions.[19,26] A significant component of chia's soluble fiber is mucilage, a complex polysaccharide that forms a hydrocolloid gel when hydrated. Mucilage contributes to the functional and technological properties of chia in food applications, acting as a natural thickening or stabilizing agent. In vitro

digestion models have investigated the impact of chia mucilage at concentrations of 3, 5, and 8 g/kg, revealing its influence on digestion dynamics and nutrient absorption. Beyond fiber, chia seeds are rich in phytochemicals such as phenolic acids and flavonoids, including chlorogenic acid, caffeic acid, quercetin, and kaempferol. These compounds exhibit strong antioxidant activity, contributing to chia's anti-inflammatory, antimicrobial, and immune-supportive properties. Collectively, these phytoconstituents play an integral role in the modulation of oxidative stress and inflammation, underscoring the seed's utility as a functional food component.[19-26]

Therapeutic application of chia seed

Nephroprotective activity

Saleem *et al.* (2020) investigated the nephroprotective and antiurolithiatic potential of chia (*Salvia hispanica*) seed extract in a rat model of experimentally induced urolithiasis. Kidney stone formation was induced through oral administration of ethylene glycol (0.75%, v/v) combined with ammonium chloride (1%, v/v) for the initial three days, followed by ethylene glycol alone for an additional 18 days. The study design included six groups: Group I served as the normal control, while Group II functioned as the disease control and received only ethylene glycol. Group III was administered, a commercially available polyherbal formulation with established antiurolithiatic properties.[27]

Experimental groups IV to VI were treated with dry chia seed extract at doses of 100, 300, and 700 mg/kg body weight, respectively, for a total of 21 days. Biochemical analysis revealed that chia seed administration significantly attenuated the elevations in serum creatinine, urea, uric acid, and total protein levels observed in the disease control group, suggesting amelioration of renal impairment. Furthermore, chia-treated rats demonstrated a marked reduction in urinary excretion of calcium, oxalate, and phosphate, indicative of decreased lithogenic risk.[27,28]

Complementary *in vitro* assays further corroborated these findings, showing that chia seed extract effectively inhibited calcium oxalate crystallization by disrupting critical steps such as nucleation, crystal growth, and aggregation. The observed protective effects were attributed primarily to the flavonoid constituents of chia seeds, particularly quercetin, which exhibits potent antioxidant activity. This antioxidative mechanism is proposed to counteract oxidative stress-related pathways involved in urolithiasis pathogenesis.[29,30]

Anti hypertensive activity

Numerous clinical investigations have substantiated the antihypertensive properties of chia seeds (*Salvia hispanica* L.), attributing these effects to their rich composition of bioactive compounds, including dietary fiber, omega-3 fatty acids, and polyphenols.

In a randomized controlled trial, Toscano *et al.* (2014) assessed the impact of chia flour supplementation on blood pressure among hypertensive individuals. Participants were allocated into three groups: medicated hypertensive patients receiving chia flour (CHIA-MD), non-medicated hypertensive patients receiving chia flour (CHIA-NM), and a placebo group. Over a

12-week period, both CHIA-MD and CHIA-NM groups exhibited significant reductions in systolic blood pressure (SBP), with the CHIA-MD group decreasing from 111.3 ± 2.2 to 100.1 ± 1.8 mmHg and the CHIA-NM group from 146.8 ± 3.8 to 137.3 ± 3.1 mmHg. No significant changes were observed in the placebo group.[31]

Complementing these findings, Vuksan *et al.* (2007) conducted a study wherein participants consumed 15 grams of ground chia seeds per 1000 kcal daily for 14 days. This intervention led to a mean reduction in SBP by 6.3 ± 4 mmHg, along with decreases in high-sensitivity C-reactive protein and von Willebrand factor levels, indicating improved cardiovascular health. [32]

Further evidence comes from Alwosais *et al.* (2021), who investigated the effects of chia seed supplementation in adults aged 21–65 with type 2 diabetes. Participants consuming 40 grams of chia seeds daily for 12 weeks experienced a significant reduction in SBP from 132 to 119 mmHg, highlighting the potential of chia seeds in managing hypertension among diabetic individuals. [33]

These studies collectively underscore the efficacy of chia seed supplementation in lowering blood pressure, suggesting its potential as a functional food in cardiovascular risk management.Several studies have highlighted the potential of chia seeds in managing high blood pressure. Vertommen *et al.* (2006) conducted a study involving individuals with hypertension who consumed 50 grams of chia seeds daily for a month. The participants experienced a noticeable decrease in systolic blood pressure (SBP), which dropped by 4.6 mmHg—from 66.1 to 61.5 mmHg.[34]

Anti diabetic activity

Chia seeds (*Salvia hispanica* L.) have garnered considerable attention for their potential benefits in the regulation of glycemic responses and the management of hyperglycemia, particularly in individuals with type 2 diabetes mellitus (T2DM) and metabolic syndrome. These seeds are rich in dietary fiber (approximately 34–40%), predominantly soluble fiber, which forms a gel-like matrix in the gastrointestinal tract, thereby slowing carbohydrate digestion and glucose absorption. This delayed absorption attenuates postprandial glucose spikes and improves overall glycemic control.[35,36] Moreover, chia seeds are a source of high-quality plant-based protein, polyunsaturated fatty acids—particularly alpha-linolenic acid (ALA)—and bioactive polyphenols, all of which contribute to enhanced insulin sensitivity and reduced oxidative stress, two key factors in the pathophysiology of hyperglycemia.

In a clinical study by Vuksan *et al.* (2010), individuals with type 2 diabetes who consumed 37 grams of chia seeds daily for 12 weeks exhibited significant improvements in glycemic markers. Fasting blood glucose and postprandial glucose levels were reduced, and HbA1c (glycated hemoglobin) levels decreased, indicating long-term glycemic improvement. Additionally, reductions in high-sensitivity C-reactive protein (hs-CRP) and systolic blood pressure were observed, suggesting that chia consumption may also confer anti-inflammatory and cardioprotective effects in hyperglycemic individuals.[37] Furthermore, Alwosais *et al.* (2021)

supplemented the diets of adults with type 2 diabetes with 40 grams of chia seeds daily for 12 weeks. In addition to a significant reduction in systolic blood pressure, notable improvements in fasting blood glucose levels were reported, reinforcing chia's role in metabolic regulation.[36,38] The hypoglycemic effects of chia are attributed to several mechanisms

- Viscous gel formation delaying gastric emptying.
- Inhibition of α-amylase and α-glucosidase enzymes, reducing carbohydrate digestion.
- Modulation of incretin hormones (e.g., GLP-1), which enhance insulin secretion.
- Improvement in insulin receptor signaling due to anti-inflammatory and antioxidant effects of phenolic compounds such as caffeic acid, chlorogenic acid, and quercetin

Immunomodulatory effects

Chia seeds possess immunomodulatory potential, offering a competitive advantage over other omega-3 polyunsaturated fatty acid (PUFA) sources in addressing conditions such as gastrointestinal discomfort, allergies, and weight regulation. Unlike marine-derived PUFAs, chia seeds and oil are free from adverse effects such as fishy aftertaste, allergic responses, and digestive disturbances, which are commonly associated with marine oils and flaxseed consumption.[39] Despite these promising findings, the immune stimulatory capacity of chia has not yet been extensively replicated or validated in further studies. Study on weaning Wistar rats, observing significantly elevated serum and thymic IgE (immunoglobulin E) levels in the group receiving a chia-based diet compared to the control group, over a 30-day period. This suggests an immune-enhancing effect. Importantly, no allergic reactions, such as dermatitis or behavioral changes, were reported in the chia-fed group, indicating its potential safety as a dietary Immunostimulant.[40]

Furthermore, Parker *et al.* (2018) demonstrated that chia supplementation resulted in similar effects to fish oil with regard to food intake, weight gain, thymus mass, thymocyte count, and IgE concentration, suggesting its comparative efficacy in modulating immune parameters.

Anti-oxidant activity

Numerous studies have confirmed that chia seeds exhibit strong antioxidant properties. Chia seed extracts significantly inhibited guaiacol enzymatic oxidation, suggesting the presence of bioactive compounds with antioxidant potential.[41] Similarly, study reported enhanced activity of antioxidant enzymes—including catalase, glutathione reductase, glutathione, and glutathione peroxidase—in obese rats fed with chia seeds or chia oil, compared to animals on a high-fructose diet.[42]

Sargi *et al.* (2013) further established that chia seeds are capable of neutralizing ABTS cation radicals, scavenging synthetic DPPH radicals, and reducing ferric ions, indicating comprehensive antioxidant capabilities that surpass those of flaxseed.[43] Segura-Campos *et al.* (2013) supported these findings, reporting over 70% neutralization of DPPH radicals and inhibition of guaiacol oxidation by chia extracts.[44]

The antioxidant potential of chia seeds has also been quantified using the Oxygen Radical Absorbance Capacity (ORAC) method. Reyes-Caudillo *et al.* (2008) evaluated the influence of

chia extract on beta-carotene degradation in a linoleic acid–beta-carotene emulsion at 50°C, finding antioxidant activity ranging from 73.5% to 79.3%, further confirming chia's ability to prevent lipid peroxidation.[45]

Anti-obesity

Animal studies have demonstrated that chia seeds and their oil can mitigate obesity and associated metabolic disturbances. According to study, administration of chia seed products to obese rodents resulted in improvements in insulin sensitivity, glucose tolerance, visceral fat reduction, hepatic lipid accumulation, myocardial and hepatic fibrosis, and systemic inflammation.[46]

One key mechanism involves the suppression of stearoyl-CoA desaturase (SCD), an enzyme that facilitates the conversion of elaidic acid to conjugated linoleic acid. Inhibition of SCD leads to enhanced oxidation of linoleic acid (C_{18}:2_n-6) in mitochondria and a reduction in the n-6/n-3 fatty acid ratio. This enzymatic regulation helps protect against lipid accumulation, obesity, and insulin resistance.[47]

Regulatory recognition and extraction characteristics of *Salvia hispanica* oil

The increasing incorporation of *Salvia hispanica* L. (chia) oil in functional foods and nutraceutical formulations has led to its official recognition by regulatory bodies. In December 2017, the United States Pharmacopeia (USP) monographed chia seed oil as a safe dietary ingredient, highlighting its nutritional and therapeutic relevance (48). As per USP specifications, chia oil must be extracted exclusively via mechanical cold-pressing techniques—explicitly prohibiting the use of external heat or organic solvents—to preserve the structural integrity of bioactive constituents such as α-linolenic acid (ALA) and natural antioxidants. Moreover, the addition of tocopherols during processing is recommended to enhance the oxidative stability and extend the shelf-life of the oil.[48,49]

The physicochemical properties of chia seed oil contribute significantly to its classification as a high-quality functional lipid source. The oil exhibits an iodine value of approximately 207, indicative of its high degree of unsaturation, along with a saponification value of 193.3. Tocopherol concentrations reach up to 480 mg/kg, while trace metal contamination remains minimal—copper and iron levels being 0.1 and 0.3 ppm, respectively. Its oxidative status is favorable, as evidenced by low peroxide (1.0 meq O_2/kg) and anisidine values (0.3 meq O_2/kg), and a Rancimat induction period of 2.3 hours, which indicates moderate resistance to oxidative degradation. Typical oil yield from cold pressing methods ranges between 35.6% and 38.6%.[50,51]

Multiple extraction technologies have been evaluated for chia oil production, each offering distinct benefits regarding yield, quality, and bioactive retention. Cold-press extraction, carried out either at ambient temperature (~4 °C) or using a controlled screw press at 25–30 °C with electrical heating, maintains superior antioxidant content but generally yields less oil (3). In contrast, solvent-based extraction using Soxhlet systems and *n*-hexane significantly improves oil recovery and enhances emulsification properties. However, this method compromises the

retention of phenolic compounds and endogenous antioxidants.[52] Supercritical fluid extraction (SFE), particularly utilizing CO_2 at 408 bar and 80 °C, is currently regarded as the most advanced and efficient method. This technique yields high-purity oil while preserving essential fatty acids such as ALA and linoleic acid (LA), thereby producing a lipid profile highly suitable for nutraceutical applications.[53]

Future Prospects

Despite the extensive research supporting the benefits of chia seeds, several areas remain open for further exploration [54,55]

- **Clinical Trials**: More large-scale, randomized controlled trials are needed to confirm the therapeutic efficacy of chia in various human populations, especially concerning its immunomodulatory and anti-obesity effects.
- **Mechanistic Studies**: Detailed mechanistic studies should be conducted to elucidate the molecular pathways through which chia exerts its metabolic, anti-inflammatory, and antioxidant effects.
- **Product Development**: Future research could focus on developing innovative chia-based functional foods, nutraceuticals, and supplements, optimizing their bioavailability and consumer acceptability.
- **Long-Term Safety**: Investigations into the long-term safety of high-dose chia consumption are warranted, particularly regarding its effects on nutrient absorption and potential drug-food interactions.
- **Agronomic Research**: Studies aimed at enhancing chia crop yields, improving phytochemical profiles through breeding programs, and ensuring sustainable cultivation practices will further strengthen its role in the global food system.
- **Bioactive Peptides and Extracts**: Isolation, characterization, and functional testing of chia-derived bioactive peptides and extracts could open new avenues for targeted therapies against metabolic and inflammatory diseases.

Discussion:

The evidence presented underscores the multifaceted health benefits of *Salvia hispanica* L., validating its classification as a functional and therapeutic food. Chia seeds offer a unique combination of soluble and insoluble fibers, essential fatty acids, and polyphenolic antioxidants that contribute to improved digestive health, lipid metabolism, and systemic inflammation control. Their mucilage content not only facilitates gastrointestinal benefits but also enhances food formulation versatility, supporting their integration into various dietary products. From a clinical standpoint, chia supplementation has demonstrated significant effects in reducing systolic blood pressure in hypertensive and diabetic populations, likely mediated through enhanced endothelial function, reduced inflammation, and favorable lipid modulation. In metabolic syndrome and type 2 diabetes contexts, chia's impact on glycemic control is notable, with multiple mechanisms—including delayed gastric emptying, inhibition of carbohydrate-hydrolyzing enzymes, and modulation of insulin sensitivity—working synergistically.

The nephroprotective properties observed in experimental urolithiasis models suggest that chia's antioxidant constituents, particularly quercetin, may mitigate oxidative damage associated with stone formation. These results highlight its potential role in renal health preservation. Moreover, chia seeds exhibit anti-obesity effects through modulation of lipid metabolism, suppression of lipogenic enzymes such as stearoyl-CoA desaturase, and enhancement of mitochondrial fatty acid oxidation. This mechanistic profile aligns with observed reductions in visceral fat and improvements in hepatic and myocardial integrity in animal models.

Chia's immunomodulatory actions, though less extensively studied, present promising prospects for managing immune-related disorders without the adverse effects commonly associated with fish-derived omega-3s. The elevation of immunoglobulin levels without eliciting allergic reactions further supports its dietary safety and efficacy. Finally, advancements in chia oil extraction—particularly supercritical CO_2 methods—enable the production of high-quality oils rich in bioactive lipids and antioxidants, expanding its applicability in nutraceutical and therapeutic contexts. The official recognition of chia oil by regulatory authorities like the USP reinforces its safety and utility. In conclusion, the comprehensive nutritional and pharmacological attributes of chia seeds position them as a valuable ally in promoting health and managing chronic diseases. Continued research and clinical validation will further elucidate their full therapeutic potential and optimize their use in functional food development.

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PHYTOSOME TECHNOLOGY FOR HERBAL BIOACTIVES: MECHANISMS, APPLICATIONS, AND FORMULATION STRATEGIES

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Abstract:

Phytosome technology is an advanced approach that enhances the therapeutic potential of herbal bioactives by improving their solubility, membrane permeability, and overall bioavailability. By forming molecular complexes between phytoconstituents and phospholipids, phytosomes offer superior pharmacokinetic profiles over conventional herbal extracts. This chapter provides a critical review of the principles, formulation strategies, and wide-ranging applications of phytosomes in various therapeutic domains, including hepatoprotection, inflammation, cardiovascular health, and oncology. It discusses various types of phytosome formulations, their advantages over traditional systems, and formulation challenges. Additionally, the chapter highlights regulatory aspects and future prospects in the development of phytosome-based herbal products in both pharmaceutical and nutraceutical sectors.

Keywords: Phytosome, Herbal Bioactives, Phospholipid Complex, Bioavailability Enhancement, Herbal Drug Delivery, Silymarin, Nano-Phytosomes,

Introduction:

Overview of herbal bioactives and their limitations

Herbal medicines have been used for centuries in traditional systems of healthcare such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani. These systems rely heavily on plant-derived bioactives such as flavonoids, alkaloids, polyphenols, and terpenoids, which exhibit a wide range of pharmacological activities, including anti-inflammatory, antioxidant, hepatoprotective, anticancer, and antimicrobial effects. However, despite their potent therapeutic potential, many herbal constituents suffer from major limitations, such as poor aqueous solubility, low membrane permeability, instability in gastrointestinal fluids, and extensive first-pass metabolism. These challenges lead to suboptimal systemic bioavailability and, consequently, reduced clinical efficacy.

For instance, curcumin from *Curcuma longa*, silymarin from *Silybum marianum*, and quercetin from various flavonoid-rich plants are all examples of bioactives with proven pharmacological actions but limited absorption and rapid elimination. Addressing these limitations is crucial for translating the therapeutic benefits of herbal actives into consistent and effective clinical outcomes.

Need for advanced delivery systems

The conventional dosage forms of herbal medicines, such as tablets, capsules, decoctions, and tinctures, often do not offer controlled or targeted release, nor do they protect unstable phytoconstituents from degradation. Furthermore, the lack of standardization and the complex nature of herbal extracts further complicate their formulation and therapeutic predictability. As the global demand for evidence-based phytomedicines increases, there is a pressing need to adopt advanced formulation technologies that can enhance the solubility, stability, and bioavailability of herbal actives while maintaining safety and patient compliance.

Recent advances in pharmaceutical technology have opened avenues for novel drug delivery systems such as nanoparticles, liposomes, micelles, and nanoemulsions. Among these, phytosome technology has emerged as a highly promising approach for herbal drug delivery due to its ability to form stable complexes that improve membrane permeability and systemic absorption.

Emergence of phytosome technology

Phytosomes are unique lipid-compatible molecular complexes formed by the interaction of standardized plant extracts or pure phytoconstituents with phospholipids, typically phosphatidylcholine. Unlike liposomes, which encapsulate the drug within a vesicle, phytosomes involve chemical interactions at the molecular level, resulting in a more stable and bioavailable complex. This intimate complexation enables phytosomes to fuse with biological membranes more efficiently, facilitating better absorption and bioefficacy.[1]

The phytosome technology was pioneered in the 1980s by Indena (Italy), and since then, numerous phytosome-based herbal formulations have been developed and patented. Silymarin phytosomes were among the first to demonstrate enhanced hepatoprotective activity due to improved bioavailability. Since then, this technology has been applied to various other plant actives, including curcumin, green tea polyphenols, ginkgo biloba extract, and grape seed proanthocyanidins.[2]

In this chapter, we aim to provide a comprehensive review of phytosome technology, focusing on its formulation strategies, types, therapeutic applications, and potential advantages over conventional delivery systems. The chapter also addresses the formulation challenges, regulatory considerations, and future research directions that will shape the development of next-generation phytosome-based herbal therapies.

Formulation strategies for phytosomes

Phytosome formulation involves the molecular complexation of phytoconstituents with phospholipids, resulting in a stable, bioavailable, and membrane-compatible system. Unlike conventional liposomes where the drug is entrapped in a vesicle, phytosomes are characterized by the formation of a true chemical complex, often via hydrogen bonding and hydrophobic interactions. The formulation process is influenced by several key parameters, including the selection of raw materials, choice of solvent system, processing method, and encapsulation strategy.

Selection of phospholipids and solvents

Phospholipids are central to phytosome formation, with phosphatidylcholine (PC) being the most widely used due to its biocompatibility, amphiphilic nature, and ability to form stable complexes. Other phospholipids such as phosphatidylethanolamine or phosphatidylserine may be used based on the desired properties of the final product.[3]

The purity and source of phospholipids (soy lecithin vs. egg lecithin) can significantly impact complexation efficiency, particle size, and bioavailability. Soy-derived phospholipids are more commonly used for commercial phytosome formulations due to their lower cost and high content of PC. Solvents play a crucial role in facilitating the interaction between the phytoconstituent and the phospholipid. Typically, polar aprotic solvents such as dichloromethane, chloroform, or acetone are used in combination with ethanol or methanol to solubilize both components. The choice of solvent system is guided by the solubility profile of the bioactive and the phospholipid, as well as regulatory acceptability and ease of solvent removal post-formulation.[4]

Process parameters: Temperature, pH, concentration

Several process variables must be optimized to ensure efficient phytosome formation and desired physicochemical characteristics:[5]

- **Temperature**: The formation of the phytoconstituent–phospholipid complex often requires moderate heating (typically 40–60°C) to facilitate solubilization and molecular interaction. Excessive heating, however, can degrade thermolabile herbal actives.
- **pH**: The ionization state of the phytoconstituent and phospholipid is pH-dependent, influencing complexation efficiency. A mildly acidic to neutral pH (around 6–7) is generally optimal for most systems.
- **Molar Ratio**: The phytoconstituent-to-phospholipid ratio significantly impacts the complexation yield and stability. Common ratios range from 1:1 to 1:2 (w/w), but this may vary based on the molecular weight and polarity of the bioactive.
- **Reaction Time**: Longer interaction times generally allow for more complete complexation, though excessive processing may lead to degradation or aggregation.

The resulting complex is usually dried by solvent evaporation, rotary evaporation, or freeze-drying to obtain a stable powder that can be used in tablets, capsules, or topical preparations.

Encapsulation and scale-up considerations

Following complexation, the phytosome complex can be encapsulated into various dosage forms such as soft gel capsules, tablets, or topical gels**.** Spray-drying or freeze-drying may be employed to convert the liquid complex into a dry powder, improving shelf-life and handling. For commercial scalability, formulation processes should be reproducible, cost-effective, and compliant with Good Manufacturing Practices (GMP)**.** Selection of GRAS (Generally Recognized as Safe) solvents and excipients, as well as minimizing residual solvent content, are critical for regulatory compliance. Moreover, incorporation of stabilizers, cryoprotectants, or co-carriers (e.g., polymers, surfactants) may enhance the stability and

performance of phytosome formulations, especially in nano-phytosomes or combination systems.[6]

Types and variants of phytosome formulations

The evolution of phytosome technology has led to the development of various formulation types, each specifically engineered to enhance the physicochemical and therapeutic performance of herbal bioactives. While the foundational principle of all phytosome systems is the formation of a molecular complex between phytoconstituents and phospholipids, these systems differ in terms of particle size, composition, fabrication techniques, and intended applications. This section discusses the major types and emerging variants of phytosome formulations that have broadened the scope and utility of this drug delivery platform.

Conventional phytosomes

Conventional phytosomes represent the earliest and most widely explored class of phytosome formulations. These systems typically involve the complexation of a standardized herbal extract or isolated phytoconstituent with phospholipids, particularly phosphatidylcholine. The resultant molecular complex demonstrates increased lipophilicity, which significantly enhances its interaction with biological membranes. This, in turn, improves gastrointestinal absorption and systemic bioavailability compared to crude herbal preparations. Numerous conventional phytosome formulations have shown superior therapeutic outcomes in both preclinical and clinical studies. For example, silymarin phytosome has demonstrated enhanced hepatoprotective activity, Ginkgo biloba phytosome has shown improved cerebral blood flow and cognitive enhancement, and green tea phytosome has been associated with better antioxidant performance due to improved systemic exposure of catechins. These conventional phytosomes are typically formulated as oral dosage forms, such as tablets or capsules, and have set a foundation for subsequent innovation in phytosome technology.[7]

Nano-phytosomes

Nano-phytosomes are an advanced generation of phytosome systems, characterized by their nanoscale particle size, typically less than 200 nanometers. Reducing the particle size to the nanometric range leads to an increased surface area, which promotes enhanced cellular uptake, improved membrane permeation, and extended systemic circulation. These attributes make nano-phytosomes particularly suitable for parenteral, transdermal, and topical routes of administration. Various size reduction techniques such as high-pressure homogenization, ultrasonication, and microfluidization are employed to produce nano-sized phytosome particles. Additionally, nano-phytosomes may be stabilized with the aid of surfactants, polymers, or co-solvents to prevent aggregation and enhance their physicochemical stability over time. These nanosystems have demonstrated substantial therapeutic potential in diverse areas, particularly in cancer and inflammatory diseases, where active or passive targeting is critical. For instance, curcumin-loaded nano-phytosomes have shown superior anticancer and anti-inflammatory effects in experimental studies compared to their conventional counterparts, owing to their improved pharmacokinetic and biodistribution profiles.[8]

Herbal phytosomes combined with polymers and surfactants

To further tailor the release kinetics, stability, and targeting efficiency of phytosome formulations, hybrid systems incorporating polymers and surfactants have been developed. Biodegradable polymers such as chitosan, alginate, and poly(lactic-co-glycolic acid) (PLGA) have been used to modify the surface or matrix of phytosomes, providing additional functionalities such as mucoadhesion, pH responsiveness, and controlled drug release. Surfactants like Tween 80 and Span 60 are also employed to enhance the solubility, dispersion stability, and skin permeation of phytosome-based formulations. These modifications have expanded the application spectrum of phytosomes beyond conventional oral delivery. For example, chitosan-coated phytosomes have demonstrated prolonged residence time on mucosal surfaces, making them highly suitable for buccal and nasal delivery routes. Similarly, polymeric nano-phytosomes have shown promising results in tumor-targeted drug delivery, with improved tissue accumulation and therapeutic efficacy. Additional applications include transdermal patches employing surfactant-enriched phytosomes to improve dermal penetration and gastroretentive systems designed with mucoadhesive polymers for sustained drug release in the stomach. These hybrid phytosome systems exemplify the potential of rational design in optimizing phytosome-based delivery platforms for diverse clinical needs.[9]

Applications in herbal drug delivery

Phytosome technology has revolutionized herbal drug delivery by addressing the major pharmacokinetic challenges that limit the clinical efficacy of many herbal bioactives. By improving aqueous solubility, membrane permeability, and systemic bioavailability, phytosomes facilitate more predictable therapeutic responses. Their ability to form lipid-compatible complexes with phytoconstituents allows for better integration into biological membranes, resulting in enhanced absorption and prolonged circulation. This section elaborates on the diverse applications of phytosome-based formulations across several therapeutic domains.

Hepatoprotective agents (e.g., silymarin)

Among the earliest and most successful applications of phytosome technology is the delivery of silymarin, a hepatoprotective flavonolignan derived from *Silybum marianum*. Silymarin has inherently poor oral bioavailability due to limited water solubility and extensive first-pass metabolism. However, when formulated as a phytosome complex, it exhibits significantly enhanced pharmacokinetic properties. Studies have shown that silymarin phytosomes achieve up to four- to ten-fold higher oral bioavailability compared to the unformulated extract. This enhancement translates to improved therapeutic outcomes, including accelerated liver cell regeneration, potent antioxidative effects, and robust hepatoprotection against toxic insults such as carbon tetrachloride and paracetamol. Clinical investigations have confirmed the efficacy of silymarin phytosome formulations in managing liver conditions such as alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and various forms of hepatitis.[10]

Anti-inflammatory and antioxidant applications (e.g., curcumin, quercetin)

Phytosome formulations have also shown remarkable success in enhancing the bioavailability of polyphenolic compounds with anti-inflammatory and antioxidant properties, such as curcumin and quercetin. Both molecules are known for their wide-ranging therapeutic effects, but their clinical application has been hampered by poor solubility and rapid metabolism. Phytosome-based delivery systems significantly enhance their absorption and systemic retention, leading to improved efficacy. For instance, curcumin phytosomes, such as the commercially available Meriva®, have demonstrated notable improvements in reducing inflammation and oxidative stress markers. These formulations have been successfully used in conditions like osteoarthritis, inflammatory bowel disease, and metabolic syndrome, where conventional curcumin extracts fail to achieve therapeutic concentrations. Similarly, quercetin phytosomes have shown enhanced anti-inflammatory activity by reducing pro-inflammatory cytokines and oxidative biomarkers in experimental and clinical models.[11]

Cardiovascular and metabolic disorders

In the realm of cardiovascular and metabolic health, phytosome technology has enabled more effective utilization of bioactives like berberine, green tea catechins, and resveratrol. These compounds are known for their lipid-lowering, antihypertensive, and insulin-sensitizing effects, yet their clinical translation has been restricted by low oral bioavailability. Phytosome formulations of these agents have demonstrated enhanced therapeutic outcomes by improving their pharmacokinetic profiles. Berberine phytosomes, for example, have shown superior efficacy in reducing LDL cholesterol and fasting blood glucose compared to conventional berberine, which is poorly absorbed in its native form. Likewise, green tea phytosomes have exhibited better endothelial protection and lipid profile modulation. These advancements have the potential to redefine phytotherapy in managing chronic conditions such as type 2 diabetes, dyslipidemia, and atherosclerosis.[12]

Anticancer therapies

Phytosome-based delivery systems have opened new avenues for the use of herbal constituents in oncology. Phytochemicals like epigallocatechin gallate (EGCG), curcumin, and boswellic acids possess anticancer potential but suffer from poor bioavailability and rapid systemic clearance. When formulated as phytosomes, these compounds demonstrate enhanced stability, improved tumor targeting, and reduced systemic toxicity. Phytosome complexes facilitate better penetration into tumor tissues, often exploiting the enhanced permeability and retention (EPR) effect. EGCG phytosomes have shown promising anticancer activity in experimental models of breast and prostate cancer, where they exhibit increased accumulation in tumor tissues and promote apoptosis while inhibiting angiogenesis. These findings highlight the potential of phytosome technology to serve as a platform for delivering plant-derived chemopreventive and chemotherapeutic agents with greater precision and efficacy.[13]

Dermatological and cosmetic uses

Phytosome formulations have also gained prominence in dermatology and cosmeceutical applications, where effective skin penetration of active ingredients is essential. The

phospholipid-based structure of phytosomes enhances their compatibility with the lipid-rich stratum corneum, facilitating deeper and more sustained dermal delivery. Various herbal actives have been successfully formulated as topical phytosomes, offering benefits such as anti-aging, anti-inflammatory, and photoprotective effects. For example, grape seed polyphenol phytosomes have demonstrated skin-firming and antioxidant properties, while licorice root phytosomes exhibit skin lightening and soothing activity. Green tea phytosomes have been particularly effective in protecting the skin against ultraviolet (UV)-induced oxidative stress. These formulations are typically developed as creams, gels, or transdermal patches, offering improved patient adherence and consistent therapeutic outcomes.[14]

Advantages and limitations of phytosomes

Phytosome technology represents a significant advancement in the formulation of herbal drugs by offering a strategy to overcome the pharmacokinetic barriers that limit the efficacy of many plant-derived bioactives. By forming molecular complexes between phytoconstituents and phospholipids, phytosomes enhance the physicochemical compatibility of herbal actives with biological membranes, which contributes to improved therapeutic outcomes. Despite its substantial advantages, the technology also has certain limitations that need to be critically evaluated for its broader implementation in clinical and industrial settings.

One of the most notable advantages of phytosomes is their ability to enhance the bioavailability of herbal constituents that are otherwise poorly absorbed due to low aqueous solubility or limited membrane permeability. The phospholipid complexation renders the phytoconstituents more lipophilic, facilitating their passage across biological barriers and resulting in increased plasma concentrations and therapeutic efficacy. This bioavailability enhancement can significantly amplify the clinical effectiveness of herbal remedies traditionally known for variable and inconsistent results.

In addition to improved absorption, phytosomes confer molecular stability to labile herbal compounds. Many phytoconstituents are sensitive to degradation in the gastrointestinal tract or undergo rapid first-pass metabolism, which reduces their therapeutic potential. Phytosome formulation helps protect these sensitive molecules from hydrolysis and enzymatic degradation, thereby extending their half-life and improving their pharmacokinetic profile. This stabilization also translates into better shelf life for finished products, particularly when formulated into solid dosage forms.

Improved therapeutic performance from phytosome formulations often allows for lower dosing, which can reduce the incidence of adverse effects and improve patient adherence. The user-friendly nature of phytosome dosage forms—ranging from oral capsules to topical creams—further supports compliance. Moreover, the adaptability of phytosome systems to multiple routes of administration, including oral, transdermal, topical, nasal, and parenteral, broadens their application scope and allows for tailored delivery strategies based on therapeutic needs.

Another compelling advantage of phytosome technology is its growing industrial and regulatory acceptance. Several phytosome-based products, such as Siliphos®, Meriva®, and

Greenselect®, have gained commercial success and regulatory approvals in various countries. These developments underscore the market viability of phytosomes, especially when formulated with excipients classified as Generally Recognized As Safe (GRAS), thus easing regulatory hurdles.[15]

Despite these strengths, phytosome technology is not without limitations. One of the major challenges lies in the high cost associated with the use of pharmaceutical-grade phospholipids and the complex manufacturing processes involved. Techniques such as solvent evaporation, freeze-drying, and particle size reduction may elevate production costs, making large-scale manufacturing less economically attractive, especially for developing markets. Another limitation is the limited water solubility of some phytosome complexes. Although their lipophilicity aids in membrane transport, poor aqueous solubility can hinder performance in water-based systems or in environments requiring rapid dissolution. This may restrict their use in certain formulation types, necessitating additional excipients or processing steps to enhance dispersibility.

A significant hurdle in phytosome development is the absence of a universal preparation methodology. Parameters such as the phospholipid-to-phytoconstituent ratio, choice of solvent, temperature, and stirring speed can drastically affect the properties of the final complex. This lack of standardization poses challenges for reproducibility, scalability, and regulatory compliance, especially when transitioning from laboratory to industrial production. Stability concerns also persist, particularly in liquid formulations. Over time, phospholipids are prone to oxidation and hydrolysis, which can compromise the integrity of the phytosome complex in aqueous environments. Such instability necessitates the use of antioxidants, stabilizers, or conversion into more stable solid dosage forms like tablets or lyophilized powders.

Finally, the regulatory classification of phytosome formulations varies significantly across jurisdictions. Depending on the country and composition, these products may be categorized as dietary supplements, nutraceuticals, or herbal medicines. This inconsistency in classification can complicate product development strategies, influence the scope of permissible therapeutic claims, and affect the extent of clinical validation required for market approval.[16]

Future prospects and research opportunities

Phytosome technology has shown significant promise in improving the pharmacokinetic profiles and therapeutic efficacy of herbal bioactives. However, the field continues to evolve, presenting numerous opportunities for further innovation and advancement. Interdisciplinary approaches involving pharmaceutical sciences, nanotechnology, systems biology, and computational modeling are expected to shape the next generation of phytosome-based drug delivery systems. These evolving strategies aim not only to improve performance but also to address longstanding challenges in formulation, standardization, and regulatory acceptance.

The integration of phytosome technology with nanotechnology is a particularly promising direction, offering the potential for targeted and controlled drug delivery. Researchers are actively exploring stimuli-responsive phytosomes that release their payload in response to specific triggers such as pH changes, enzymatic activity, or oxidative stress. This approach can

lead to site-specific drug release, reducing off-target effects and enhancing therapeutic outcomes. Ligand-conjugated phytosomes, designed to target overexpressed receptors on diseased cells, are gaining attention for their utility in cancer and inflammatory diseases. Furthermore, hybrid nanosystems that combine phytosomes with other nanocarriers—such as liposomes, solid lipid nanoparticles, or polymeric micelles—can improve drug loading, release modulation, and overall stability, opening up exciting applications in oncology, neurology, and immunotherapy.

Another important frontier is the application of phytosome technology in personalized and precision herbal medicine. With growing interest in tailoring therapies to individual patient profiles, there is a need to develop phytosome formulations that accommodate genetic and metabolic variations. This involves conducting pharmacogenomic studies to understand differences in how individuals metabolize phytoconstituents and designing formulations accordingly. The use of artificial intelligence and in silico modeling can further support this goal by predicting optimal formulation parameters and therapeutic outcomes based on patient-specific data. This personalized approach is particularly relevant in managing chronic diseases such as diabetes, cardiovascular disorders, and autoimmune conditions, where interindividual variability significantly impacts treatment efficacy.

Despite advancements in formulation science, the clinical translation of phytosome-based products requires greater regulatory harmonization and robust clinical validation. Currently, there is a lack of standardized protocols for formulation, characterization, and quality control, which poses challenges for product reproducibility and regulatory approval. To facilitate wider clinical adoption, collaborative efforts between academia, industry, and regulatory agencies must focus on developing uniform guidelines and conducting large-scale clinical trials to demonstrate safety and efficacy. Establishing clear regulatory classifications—whether as dietary supplements, herbal medicines, or phytopharmaceuticals—is also essential for streamlining approval pathways across different countries and ensuring consistent product labeling and claims.

In terms of expanding the therapeutic utility of phytosomes, there is considerable potential in exploring underutilized herbal bioactives from traditional medicine systems such as Ayurveda, Traditional Chinese Medicine (TCM), and ethnomedicine. Many of these herbs possess strong pharmacological properties but remain inadequately explored due to poor pharmacokinetics. Phytosome technology offers a platform to unlock their therapeutic potential by enhancing their solubility, permeability, and bioavailability. Future research should focus on the standardization of these herbal extracts and their incorporation into phytosome-based systems. In addition, polyherbal-phytosome combinations may offer synergistic effects, supporting multitargeted approaches in the treatment of complex diseases.

As global attention shifts toward environmentally sustainable pharmaceutical practices, there is a rising interest in adopting green and eco-friendly formulation approaches in phytosome development. This includes using biodegradable and plant-based phospholipids, selecting green solvents like ethanol and ethyl lactate, and implementing solvent-free or low-energy processing

methods. Embracing such strategies not only minimizes the environmental impact of production but also aligns with the preferences of health-conscious and environmentally aware consumers.

Finally, the application of artificial intelligence and computational modeling is poised to transform phytosome research and development. Machine learning algorithms and molecular docking tools can be employed to predict the compatibility between phytoconstituents and various phospholipids, allowing for a more rational selection of formulation components. These tools can also aid in optimizing process parameters, predicting stability profiles, and screening formulations with higher throughput and accuracy. The adoption of AI-driven approaches will significantly accelerate the development of next-generation phytosome systems, ensuring higher precision, efficiency, and reproducibility in both research and commercial production.[17]

Conclusion:

Phytosome technology represents a transformative advancement in the field of herbal drug formulation, addressing long-standing challenges associated with the poor bioavailability, stability, and therapeutic consistency of herbal bioactives. By forming molecular complexes with phospholipids, phytosomes improve the solubility, membrane permeability, and systemic absorption of phytoconstituents, thereby enhancing their clinical potential. This review has highlighted the key aspects of phytosome technology — from its fundamental mechanisms and formulation strategies to its diverse applications in hepatoprotection, oncology, inflammation, dermatology, and metabolic disorders. Emerging variants such as nano-phytosomes and hybrid systems underscore the adaptability of this platform across multiple routes of administration and therapeutic indications. Despite notable advantages, challenges such as high formulation cost, stability concerns, and regulatory ambiguity must be addressed to enable broader acceptance and commercialization. Future prospects lie in the integration of nanotechnology, personalized medicine, and green formulation techniques, alongside the application of artificial intelligence for predictive modeling and optimization. In conclusion, phytosome technology offers a promising, scientifically validated approach for enhancing the therapeutic efficacy of herbal medicines. Continued interdisciplinary research and collaboration between academia, industry, and regulatory bodies will be pivotal in unlocking its full potential in modern healthcare.

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HERBAL PLANTS AS ANTIMUTAGENS: EXPLORING NATURE'S DEFENSE AGAINST GENETIC MUTATION

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Abstract:

This chapter explores the critical role of herbal plants as natural antimutagens, offering a defense against genetic mutations that are fundamental to aging and diseases like cancer. It begins by defining mutagenesis, outlining its causes from spontaneous errors to environmental mutagens, and emphasizing the necessity for antimutagenic strategies to protect genetic integrity. The text then delves into the rich historical use of medicinal plants across diverse cultures, highlighting how this traditional knowledge formed the empirical basis for modern scientific inquiry into plant bioactivity. The core of the chapter focuses on the scientific investigation of plant-derived antimutagens, detailing various classes of bioactive compounds such as flavonoids, phenolic acids, carotenoids, tannins, saponins, and alkaloids. It elaborates on the multifaceted mechanisms by which these phytochemicals exert their protective effects, including the direct inactivation of mutagens (desmutagenesis), modulation of metabolic enzymes involved in detoxification, direct protection of DNA from damage, enhancement of cellular DNA repair systems, and regulation of crucial cellular processes like apoptosis and cell cycle control. The chapter concludes by emphasizing the synergistic interactions among these compounds and the potential of herbal plants as valuable resources for developing preventive healthcare strategies based on natural antimutagens, bridging the gap between ancient traditions and modern scientific understanding.

Keywords: Herbal Plants, Antimutagenesis, Bioactive Compounds, DNA Protection

Introduction:

Mutagenesis and the need for antimutagens

Mutagenesis refers to the process by which the genetic material (DNA or RNA) of an organism is altered, resulting in a mutation.[1] These alterations can range from single nucleotide changes (point mutations) to large chromosomal rearrangements.[2] Mutations can occur spontaneously due to errors during DNA replication or repair, or they can be induced by external agents called mutagens.[3]

Mutagens are diverse and include physical agents like ultraviolet (UV) and ionizing radiation, chemical substances found in the environment, food, and industrial products (e.g., polycyclic aromatic hydrocarbons, aromatic amines, alkylating agents), and biological agents

such as viruses.[4,5] Exposure to mutagens can lead to DNA damage that, if not accurately repaired, becomes fixed as a mutation.

The consequences of mutations can be varied. While some mutations may be neutral or even beneficial (providing genetic variation for evolution), many are deleterious.[6] Accumulation of mutations in somatic cells is a key factor in aging and the development of various diseases, most notably cancer. Mutations in germline cells can be inherited, leading to genetic disorders. Given the potential for mutations to cause significant health problems, there is a critical need to understand and mitigate their occurrence.

This is where antimutagens come into play. Antimutagenesis refers to the process by which the frequency of mutations is reduced. Antimutagenic agents are substances or processes that can prevent or reverse the mutagenic effects of physical, chemical, or biological agents. These agents can act through various mechanisms, such as deactivating mutagens before they reach the DNA (desmutagenesis) or suppressing the mutation process after DNA damage has occurred (bio-antimutagenesis), often by enhancing DNA repair or modulating cellular responses. Identifying and utilizing natural or synthetic antimutagens is crucial for strategies aimed at preventing mutation-related diseases and protecting genetic integrity. Natural sources, particularly plants, have been extensively studied for their potential antimutagenic properties due to the presence of various bioactive compounds.

Historical use of medicinal plants and the scientific investigation of antimutagenesis

The use of plants for medicinal purposes is a practice as old as humanity itself, deeply interwoven with the cultural, spiritual, and practical lives of diverse societies across the globe.[7] Before the advent of modern synthetic pharmaceuticals, the plant kingdom served as the primary, if not sole, source of therapeutic agents. This extensive history of empirical observation and accumulated knowledge, passed down through generations, laid the groundwork for the scientific exploration of plant bioactivity, including the investigation of properties relevant to preventing genetic damage and mutation.

Evidence of medicinal plant use dates back tens of thousands of years. Archaeological findings, such as those from Neanderthal burial sites, suggest the deliberate collection and use of plants with known medicinal properties.[8] Ancient civilizations in Mesopotamia, Egypt, India, and China developed sophisticated systems of medicine heavily reliant on botanical remedies, documenting their uses on clay tablets, papyri, and early texts.[9, 10] The Ebers Papyrus from ancient Egypt (circa 1550 BCE), for instance, lists hundreds of remedies derived from plants.[11] Similarly, the *Huangdi Neijing* (The Yellow Emperor's Classic of Medicine), compiled in China over two millennia ago, details the therapeutic applications of numerous herbs, forming the basis of Traditional Chinese Medicine (TCM).[12] In India, the ancient system of Ayurveda, with roots extending back thousands of years, provides comprehensive descriptions of medicinal plants and their uses, many of which are still employed today.[13] Indigenous cultures across continents – from the Americas to Africa, Australia, and beyond – developed their unique pharmacopoeias

based on the local flora, demonstrating a profound understanding of plant properties through trial and error over vast periods.[14]

These traditional systems, while often intertwined with spiritual beliefs and lacking a modern understanding of disease mechanisms, were remarkably effective in treating a wide range of ailments. Remedies were developed for everything from wound healing and pain relief to treating digestive issues, infections, and chronic conditions. The efficacy observed in many cases was a testament to the presence of biologically active compounds within these plants, capable of interacting with human physiology.[15]

The transition from purely traditional use to scientific investigation began gradually, accelerating significantly with the rise of chemistry and pharmacology in the 18th and 19th centuries. Scientists started isolating pure compounds from medicinal plants that were known for their therapeutic effects. Iconic examples include the isolation of morphine from the opium poppy (*Papaver somniferum*) in the early 19th century, quinine from the cinchona bark (*Cinchona* species) for malaria, and later, aspirin (acetylsalicylic acid) derived from compounds originally found in willow bark (*Salix* species).[16] This period marked a shift from using crude plant preparations to identifying the specific molecules responsible for their observed activities, paving the way for modern drug discovery.[17]

The scientific investigation into the potential of medicinal plants to prevent genetic mutation is a more recent development, gaining significant momentum in the latter half of the 20th century. As the understanding of DNA as the carrier of genetic information solidified and the link between DNA damage, mutations, and diseases like cancer became clearer, researchers began to explore natural substances that could protect against these processes. The long history of medicinal plant use provided a rich starting point for this search. Plants that were traditionally used to treat conditions now understood to involve cellular damage or abnormal growth (such as certain types of inflammation or tumors) became prime candidates for investigation into their antimutagenic and anticarcinogenic properties.[18]

The rationale was that if plants possessed compounds capable of influencing complex biological processes to alleviate symptoms or cure diseases as observed in traditional practice, they might also contain agents capable of interfering with the process of mutagenesis. This hypothesis was supported by the growing knowledge of plant secondary metabolites-compounds not directly involved in the plant's primary growth and reproduction but often serving defensive roles against environmental stressors, pathogens, and predators. Many of these secondary metabolites, such as flavonoids, phenolic acids, carotenoids, and alkaloids, were found to possess antioxidant, anti-inflammatory, and other properties that could indirectly or directly protect cellular components, including DNA, from damage.

Early scientific investigations into the antimutagenic potential of plants often employed *in vitro* assays, such as the Ames test, which uses bacteria to detect substances that cause mutations. These studies provided initial evidence that extracts from various plants could indeed reduce the frequency of mutations induced by known mutagens.[19] For example, studies on

extracts from common dietary plants like vegetables and fruits, long associated with reduced cancer risk in epidemiological studies, demonstrated significant antimutagenic activity.[20, 21] This reinforced the idea that traditional dietary patterns rich in plant-based foods might confer protection against genetic damage.[22]

Further research involved isolating specific compounds from plants that showed promising antimutagenic activity in crude extracts. This led to the identification of numerous phytochemicals with demonstrable effects on mutagenic processes. Curcumin from turmeric (*Curcuma longa*), catechins from green tea (*Camellia sinensis*), resveratrol from grapes (*Vitis vinifera*), sulforaphane from broccoli (*Brassica oleracea*), and various flavonoids found in fruits and vegetables are just a few examples of plant-derived compounds that have been extensively studied for their ability to prevent mutations through diverse mechanisms, including scavenging free radicals, modulating enzyme activity involved in mutagen metabolism, and enhancing DNA repair.[23]

The scientific investigation has also sought to understand the mechanisms by which these plant compounds exert their antimutagenic effects, moving beyond simple observation to detailed molecular analysis. Research has revealed that these mechanisms are often multifaceted and can involve complex interactions within the cell.[24] For instance, some compounds might directly bind to and inactivate mutagens (desmutagenesis), while others might influence cellular pathways that repair damaged DNA or eliminate cells with irreparable damage (bio-antimutagenesis).

The vast and ancient history of using medicinal plants in diverse cultures has served as an invaluable reservoir of knowledge, providing leads for modern scientific inquiry.[25] The observed health benefits and therapeutic effects in traditional practices spurred scientists to investigate the underlying bioactivity of plants. This investigation, particularly with the growing understanding of genetics and disease, naturally extended to exploring the potential of plants to prevent genetic damage. The scientific validation of the antimutagenic properties of numerous plant extracts and isolated compounds has not only confirmed some traditional beliefs regarding the health-promoting aspects of plant-based diets and remedies but has also opened new avenues for developing natural strategies to protect against mutations and reduce the risk of associated diseases.[26] The legacy of traditional plant use continues to inspire and inform the search for novel therapeutic and preventive agents in the modern era.

Bioactive compounds responsible for antimutagenic effects in herbal plants

Herbal plants, long revered in traditional medicine for their therapeutic properties, owe their diverse health benefits to an array of naturally occurring substances known as bioactive compounds or phytochemicals.[27] These compounds are not essential for the plant's primary metabolic functions like growth and reproduction but often play crucial roles in defense against environmental stressors, pathogens, and herbivores.[28] The vast chemical diversity of these secondary metabolites makes plants a rich reservoir for potential medicinal agents, including those with the capacity to protect against genetic damage and mutation.[29] The scientific

investigation into the antimutagenic potential of herbal plants has increasingly focused on identifying and characterizing these specific bioactive compounds and understanding the mechanisms by which they exert their protective effects.[30]

Mutagenesis, the process of altering the genetic material, is a fundamental concern in biology and human health dueably to its association with aging, genetic disorders, and the initiation of diseases like cancer.[31] Exposure to various physical, chemical, and biological mutagens in the environment can induce DNA damage, leading to mutations if not efficiently repaired.[32] Bioactive compounds from plants can intervene in this process at multiple stages, acting as antimutagens to reduce the frequency of these harmful genetic changes.[33] Their mechanisms are varied and often synergistic, involving direct interaction with mutagens, modulation of metabolic enzymes, protection of DNA from damage, and enhancement of cellular repair systems.[34]

The most prominent classes of bioactive compounds with demonstrated antimutagenic activity are described below:

Flavonoids are ubiquitous plant pigments are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine.[35,36] Structurally, they are characterized by a diphenylpropane skeleton (C6-C3-C6) and are often present as glycosides.[37] Flavonoids exhibit a wide range of biological activities, including potent antioxidant and anti-inflammatory properties, which are key contributors to their antimutagenic effects.[38] As antioxidants, they can directly scavenge reactive oxygen species (ROS) and other free radicals that can cause oxidative damage to DNA.[39] They can also chelate metal ions that catalyze the formation of these damaging species.[40] Furthermore, certain flavonoids can modulate the activity of enzymes involved in the metabolism of xenobiotics, including pro-mutagens, either inhibiting enzymes that activate them or inducing enzymes that detoxify them.[41] Examples of flavonoids with reported antimutagenic activity include quercetin (found in onions, apples), catechin (green tea), epicatechin (cocoa, tea), and genistein (soybeans).[42,43]

Phenolic acids are another major group of plant compounds with significant antimutagenic potential.[44] These compounds contain a phenolic ring and an organic carboxylic acid group and are widely distributed in fruits, vegetables, cereals, and beverages.[45] Common examples include gallic acid, caffeic acid, ferulic acid, and ellagic acid.[46] Similar to flavonoids, phenolic acids are strong antioxidants and free radical scavengers, protecting DNA from oxidative damage.[47] Ellagic acid, found in berries and nuts, is particularly well-studied for its ability to form adducts with DNA, effectively blocking the binding sites for certain carcinogens and mutagens.[48] They can also influence enzyme systems involved in detoxification, such as glutathione S-transferases, thereby enhancing the elimination of harmful substances.[49]

Carotenoids, the pigments responsible for the vibrant yellow, orange, and red colors in many fruits and vegetables, are also recognized for their antimutagenic properties.[50]

Beta-carotene, lycopene, lutein, and zeaxanthin are well-known examples.[51] Their antimutagenic activity is primarily linked to their powerful antioxidant capacity, particularly their ability to quench singlet oxygen and scavenge peroxyl radicals.[52] By neutralizing these reactive species, carotenoids help prevent oxidative DNA damage, a major source of spontaneous and induced mutations.[53] Chlorophyllin, a semi-synthetic derivative of chlorophyll found in green leafy vegetables like spinach and coriander, has also shown significant antimutagenic activity, partly by forming complexes with mutagens in the digestive tract, preventing their absorption and interaction with DNA.[54]

Tannins are a diverse group of polyphenols found in various plant parts, known for their astringent properties.[55] They are classified into hydrolyzable tannins and condensed tannins (proanthocyanidins).[56] Tannins exhibit antimutagenic effects through several mechanisms, including antioxidant activity and the ability to precipitate proteins, which can affect the activity of enzymes involved in mutagen activation or DNA repair.[57] Some tannins can also directly interact with mutagens, forming inactive complexes.[58] The presence of tannins in plants like hawthorn (*Crataegus sanguinea*) and *Maytenus ilicifolia* is thought to contribute to their observed antimutagenic effects.[59]

Saponins are glycosides of steroids, triterpenes, or steroid alkaloids, found in a wide variety of plants.[60] They are known for their soap-like foaming properties. While some saponins can be toxic at high concentrations, many exhibit beneficial biological activities, including antimutagenic effects.[61] The mechanisms are not fully elucidated but may involve modulation of cell membrane permeability, interaction with DNA, or influencing enzyme activity.[62] Avicins, triterpenoid saponins from *Acacia victoriae*, have been shown to suppress mutations and induce apoptosis in damaged cells, highlighting the potential of this class of compounds.[63]

Alkaloids are a large group of nitrogen-containing compounds with diverse and often potent pharmacological activities.[64] While some alkaloids are known for their toxicity, others, like those found in certain medicinal plants, have shown antimutagenic properties.[65] The mechanisms can vary widely depending on the specific alkaloid structure, potentially involving intercalation with DNA, inhibition of enzymes, or antioxidant effects.[66] Further research is needed to fully understand the antimutagenic potential and safety profiles of various plant alkaloids.

Beyond these major classes, numerous other bioactive compounds contribute to the antimutagenic potential of herbal plants. These include:

- **Organosulfur compounds:** Found in garlic (*Allium sativum*) and onions (*Allium cepa*), these compounds can modulate detoxification enzymes and scavenge free radicals.[67]
- **Glucosinolates and isothiocyanates:** Present in cruciferous vegetables like broccoli (*Brassica oleracea*), these compounds are potent inducers of phase II detoxification enzymes, which help eliminate mutagens from the body.[68] Sulforaphane is a well-known example.

- **Coumarins:** These aromatic compounds found in various plants, including citrus fruits and some herbs, have shown antioxidant and enzyme-modulating activities with potential antimutagenic effects.[69]
- **Terpenoids:** A large and diverse class of compounds, including monoterpenes, diterpenes, and triterpenes, found in essential oils and resins. Some terpenoids have demonstrated antimutagenic activity through antioxidant or enzyme-modulating mechanisms.[70]

The antimutagenic effects of whole plant extracts are often attributed to the synergistic interactions between multiple bioactive compounds rather than the action of a single component.[71] This complex interplay can lead to enhanced protective effects compared to isolated compounds.[72] For example, the combination of different antioxidants in a plant extract may provide broader protection against various types of free radicals.[73] Similarly, compounds that modulate different detoxification pathways can work together to more effectively eliminate mutagens.[74]

While the scientific evidence supporting the antimutagenic potential of many plants bioactive compounds is growing, it is important to note that the efficacy can depend on various factors, including the plant species, the part of the plant used, extraction methods, dosage, and the type of mutagen involved.[75] Furthermore, some plant compounds can exhibit pro-mutagenic effects under certain conditions or at high concentrations, highlighting the need for careful research and understanding of dose-response relationships.[76]

The rich array of bioactive compounds found in herbal plants represents a significant natural resource for potential antimutagenic agents. Flavonoids, phenolic acids, carotenoids, tannins, saponins, and various other phytochemicals contribute to the protective effects observed in many plant extracts. These compounds act through diverse mechanisms, including antioxidant defense, modulation of metabolic enzymes, direct interaction with mutagens, and enhancement of DNA repair processes. Continued research into the identification, characterization, and mechanisms of action of these plant-derived compounds is crucial for developing effective natural strategies to prevent genetic mutations and reduce the risk of associated diseases, further validating the long-standing traditional use of medicinal plants for health and well-being.

Mechanisms of antimutagenesis by herbal plants

Genetic mutations, permanent alterations to the DNA sequence, are fundamental events with profound implications for biological systems and human health.[77] While some mutations are spontaneous, many are induced by exposure to environmental mutagens, including chemicals, radiation, and biological agents.[78] The accumulation of mutations is a driving force behind aging and the development of numerous diseases, most notably cancer.[79,80] Consequently, identifying and understanding agents that can prevent or reduce the frequency of mutations, known as antimutagens, is a critical area of research.[81] Herbal plants, with their rich diversity of bioactive compounds, have long been recognized in traditional medicine for their health-promoting properties, and modern scientific investigation is increasingly revealing their potential as natural antimutagens.[82,83] The protective effects of these plants are mediated

through a variety of complex mechanisms, often involving the synergistic action of multiple phytochemicals.[84]

The mechanisms of antimutagenesis can broadly be categorized based on when and how they intercept the mutagenic process.[85] Desmutagenesis involves the inactivation of mutagens before they can interact with DNA, while bio-antimutagenesis involves suppressing the mutation process after DNA damage has occurred, often by influencing cellular processes like DNA repair or replication.[86] Herbal plants and their constituent compounds employ strategies that fall into both categories, providing a multifaceted defense against genetic damage.

One primary mechanism is the direct inactivation or scavenging of mutagens (desmutagenesis).[87] Many chemical mutagens are reactive molecules or become reactive after metabolic activation. Bioactive compounds from plants, particularly those with antioxidant properties, can directly interact with these mutagens, neutralizing them before they reach the DNA.[88] For instance, phenolic compounds and flavonoids, abundant in many fruits, vegetables, and herbs, are potent free radical scavengers. They can donate electrons or hydrogen atoms to reactive oxygen species (ROS) and other free radicals generated by various mutagens or normal cellular metabolism, thereby stabilizing these damaging molecules and preventing them from attacking DNA.[89,90] Carotenoids like beta-carotene and lycopene are particularly effective at quenching singlet oxygen, another highly reactive species that can cause DNA damage.[91] Beyond free radical scavenging, some plant compounds can form stable complexes with mutagens, preventing their absorption or facilitating their excretion from the body.[92] Chlorophyllin, derived from chlorophyll in green plants, is a notable example, known to bind to planar aromatic mutagens like aflatoxins and polycyclic aromatic hydrocarbons in the gastrointestinal tract, reducing their bioavailability and subsequent interaction with DNA.[93]

Another crucial mechanism involves the modulation of metabolic enzymes responsible for the activation and detoxification of xenobiotics, including many chemical mutagens.[94] Many environmental chemicals are not directly mutagenic but are converted into reactive, mutagenic forms by phase I enzymes, primarily members of the cytochrome P450 (CYP) superfamily, in the liver and other tissues.[95] Conversely, phase II enzymes, such as glutathione S-transferases (GSTs), UDP-glucuronosyltransferases (UGTs), and NAD(P)H:quinone oxidoreductase (NQO1), are involved in conjugating mutagens or their activated metabolites with endogenous molecules, making them less reactive and more easily excretable.[96] Bioactive compounds from plants can influence the activity of these enzymes, thereby altering the balance between mutagen activation and detoxification.[97] Some phytochemicals, such as certain flavonoids and indoles (found in cruciferous vegetables), can inhibit phase I enzymes, reducing the formation of activated mutagens.[98] Others, like sulforaphane (from broccoli) and curcumin (from turmeric), are potent inducers of phase II enzymes, enhancing the detoxification and elimination of mutagens.[99,100] By shifting the metabolic balance towards detoxification, these plant compounds effectively reduce the cellular exposure to mutagenic species.[101]

Protection of DNA from damage is another critical mode of action for plant antimutagens.[102] Beyond scavenging free radicals, some plant compounds can physically interact with DNA to protect it from damage. Certain planar aromatic compounds, including some flavonoids and alkaloids, can intercalate into the DNA double helix, inserting themselves between base pairs.[103] This intercalation can stabilize the DNA structure and physically block the access of some mutagens to their target sites on the DNA molecule.[104] Additionally, some compounds can bind to the surface of the DNA or associate with chromatin proteins, providing a protective shield against damaging agents.[105] Ellagic acid, a phenolic acid found in berries and nuts, is known to form adducts with DNA, which can mask the binding sites for certain carcinogens, thus preventing the formation of mutagenic DNA adducts.[106]

Furthermore, plant bioactive compounds can enhance the cell's intrinsic ability to repair damaged DNA.[107] DNA repair pathways are essential for maintaining genomic integrity, constantly monitoring and correcting errors and damage in the DNA sequence.[108] Various types of DNA damage, including base modifications, mismatches, and strand breaks, are recognized and repaired by specific enzymatic systems.[109] Some phytochemicals have been shown to upregulate the expression or enhance the activity of key DNA repair enzymes.[110] By promoting efficient DNA repair, these compounds reduce the likelihood that DNA lesions will persist and be converted into permanent mutations during replication.[111] This represents a significant bio-antimutagenic mechanism, acting after the initial damage has occurred.[112]

Finally, some plant compounds can influence cellular processes that are crucial for preventing the propagation of mutated cells, such as apoptosis (programmed cell death) and cell cycle control.[113] Cells with significant or irreparable DNA damage can be eliminated through apoptosis, preventing them from dividing and potentially giving rise to a population of mutated cells.[114] Certain plant compounds can induce apoptosis in damaged or pre-cancerous cells.[115] This selective elimination of compromised cells serves as a critical barrier against the accumulation of mutations and the development of malignancy.[116] Additionally, plant compounds can influence cell cycle checkpoints, which are regulatory mechanisms that halt cell division if DNA damage is detected, allowing time for repair.[117] By reinforcing these checkpoints, phytochemicals can ensure that cells with damaged DNA do not proceed through the cell cycle and replicate the damaged template, thus preventing the fixation of mutations.[118]

In summary, the antimutagenic activity of herbal plants is a complex phenomenon mediated by a diverse array of bioactive compounds acting through multiple, often overlapping, mechanisms. These include the direct neutralization of mutagens, modulation of metabolic pathways to favor detoxification, physical protection of DNA, enhancement of DNA repair systems, and the regulation of cellular processes like apoptosis and cell cycle control.[119,120] The synergistic interactions between different compounds within a single plant extract can further amplify these protective effects.[121] While traditional knowledge has long pointed to the health benefits of these plants, modern scientific research is systematically unraveling the intricate molecular mechanisms by which they defend against genetic mutation, highlighting their

potential as valuable resources for preventive healthcare strategies.[122,123] Continued investigation is essential to fully understand the potential of these natural antimutagens and translate this knowledge into effective applications for human health.[124-126]

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HERBAL ANTIVIRALS: A NATURAL STRATEGY AGAINST EMERGING VIRAL DISEASES

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Abstract:

The global resurgence of viral infections including outbreaks caused by coronaviruses, dengue virus, Zika virus, influenza and other emerging pathogens has highlighted the urgent need for effective antiviral agents. The limited efficacy, high cost, and adverse effects associated with many conventional antiviral drugs underscore the necessity for alternative approaches. Herbal medicines, with their rich repository of bioactive phytochemicals such as flavonoids, alkaloids, terpenoids, and polyphenols, offer a promising natural strategy for combating viral diseases. Traditional medicinal systems like Ayurveda, Traditional Chinese Medicine (TCM), and ethnomedicine have long utilized herbal preparations for the management of viral infections. Recent pharmacological studies have validated the antiviral activities of several plant species, including Andrographis paniculata, *Glycyrrhiza glabra*, *Curcuma longa*, *Azadirachta indica and Tinospora cordifolia.* These botanicals exhibit broad-spectrum antiviral effects through diverse mechanisms such as inhibition of viral entry, replication, assembly, and modulation of host immune responses. Furthermore, advancements in extraction technologies, nanoformulations, and molecular docking studies are enhancing the bioavailability and therapeutic efficacy of these herbal antivirals. This chapter explores the scientific basis, pharmacological mechanisms, and clinical potential of herbal antivirals against emerging viral infections. It also addresses the challenges related to standardization, safety, regulatory aspects, and integration with modern therapy. Emphasizing a multidisciplinary approach, this chapter advocates for the incorporation of herbal antivirals in global antiviral strategies.

Keywords: Herbal Antivirals, Phytochemicals, Viral Infections, Traditional Medicine, Immunomodulation, Nanoformulation

Introduction:

Over the past few decades, the global health landscape has been increasingly threatened by the rise in the frequency, diversity, and severity of viral outbreaks. These outbreaks, often driven by zoonotic spillover, climate change, increased human mobility, and environmental disruption, have culminated in significant public health emergencies. Prominent examples include COVID-19, dengue fever, Zika virus infection, Ebola virus disease, Middle East Respiratory Syndrome (MERS), and avian influenza. Many of these viral diseases are either newly emergent or represent a resurgence of previously contained pathogens. The consequences of such outbreaks extend beyond human health, affecting socioeconomic stability, straining healthcare infrastructure, and disrupting global supply chains. While modern virology and

pharmaceutical science have made remarkable strides in understanding viral pathogenesis and developing targeted antiviral therapies, current treatment options face considerable limitations.[1] These include limited spectrum of activity, development of viral resistance, toxic side effects, long treatment durations, and high production costs. Moreover, the time-intensive process of antiviral drug development and regulatory approval often lags behind the pace of viral evolution and transmission.

In this challenging context, herbal medicines present a compelling avenue for exploration as both primary therapeutic agents and adjuncts to conventional antiviral therapies. Traditionally used in medical systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani, herbal remedies encompass a vast diversity of phytochemicals with documented antiviral, immunomodulatory, and anti-inflammatory properties. Recent scientific investigations have corroborated the antiviral potential of numerous plant-derived compounds, unveiling multiple mechanisms of action including inhibition of viral entry, replication, and modulation of host immune responses. Given their broad-spectrum activity, biocompatibility, and low propensity for resistance development, herbal antivirals are gaining traction as a sustainable and integrative strategy in combating emerging viral threats. This chapter delves into the growing body of evidence supporting herbal antivirals, their traditional foundations, molecular mechanisms, and future prospects in the realm of viral disease prevention and treatment.[2]

Overview of emerging viral diseases

Emerging viral diseases are defined as infections caused by viruses that have either newly appeared in a population or are rapidly increasing in incidence or geographic range. These diseases pose a significant threat to public health due to their potential for widespread transmission, high morbidity or mortality rates, and limited therapeutic options. A multitude of factors contribute to the emergence and re-emergence of these viral threats, including ecological disruption, deforestation, urbanization, climate change, globalization, and increased human-animal interaction.[3] Many emerging viruses originate from zoonotic sources, crossing the species barrier from animals to humans and often adapting rapidly to human hosts.

COVID-19 (SARS-CoV-2)

The most prominent recent example of a viral pandemic is Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First identified in Wuhan, China, in December 2019, the virus quickly spread across continents, prompting the World Health Organization (WHO) to declare a global pandemic in March 2020. Characterized by symptoms ranging from mild respiratory distress to severe pneumonia and acute respiratory distress syndrome (ARDS), COVID-19 resulted in millions of deaths, overwhelmed healthcare systems, and triggered profound social and economic disruption.[4]

SARS-CoV-2 primarily transmits through respiratory droplets, aerosols, and surface contact, and its basic reproduction number (R_0) in early waves ranged between 2 and 3, indicating high transmissibility. The virus also demonstrated the capacity for genomic mutations, leading to the emergence of multiple variants (e.g., alpha, delta, omicron), some of which exhibited increased infectivity and immune escape potential. During the initial phase of the

pandemic, the absence of effective antiviral drugs and vaccines laid bare the vulnerabilities in global health preparedness.[5] Although mRNA and vector-based vaccines were developed at unprecedented speed, global inequities in distribution and uptake, alongside issues of vaccine hesitancy and waning immunity, complicated efforts to achieve universal protection. As a result, interest surged in supportive therapies and preventive measures, including herbal remedies with antiviral and immunomodulatory properties, such as *Andrographis paniculata*, *Glycyrrhiza glabra*, and *Withania somnifera*. These botanicals were explored both in ethnomedicine and formal research settings for their potential to alleviate symptoms, reduce viral replication, or enhance host immunity.[6]

Zika virus

Zika virus, a member of the *Flaviviridae* family, was first isolated in 1947 in Uganda's Zika Forest but remained relatively obscure until the explosive outbreaks in South and Central America during 2015–2016. Transmitted primarily by *Aedes aegypti* mosquitoes, Zika infection is generally asymptomatic or causes mild symptoms such as fever, rash, conjunctivitis, and arthralgia in adults. However, the virus garnered international alarm when it was conclusively linked to severe congenital abnormalities, particularly microcephaly and other neurological disorders in newborns, a condition now recognized as congenital Zika syndrome.[7] Zika virus can also be transmitted via sexual contact, blood transfusions, and from mother to fetus during pregnancy, making containment more complex. To date, no specific antiviral treatment or vaccine exists, and management relies heavily on vector control, public awareness, and symptomatic treatment. This has led researchers to explore traditional and herbal alternatives with mosquito-repellent or antiviral properties, such as citronella, neem, tulsi (*Ocimum sanctum*), and eucalyptus, which are used in endemic regions.[8]

Dengue and Chikungunya viruses

Dengue and chikungunya are two arthropod-borne viral infections (arboviruses) that have seen a dramatic increase in global incidence over the past few decades. Both are transmitted primarily by *Aedes aegypti* and *Aedes albopictus* mosquitoes and are endemic in over 100 countries, predominantly in tropical and subtropical climates. Dengue virus (DENV), another *Flavivirus*, exists in four distinct serotypes (DENV-1 to DENV-4). While primary infection may cause a self-limiting febrile illness, secondary infection with a different serotype significantly increases the risk of dengue hemorrhagic fever and dengue shock syndrome, which can be fatal. There is currently no universally effective antiviral or fully safe vaccine, and treatment remains supportive.[9,10]

Chikungunya virus (CHIKV), a *Togavirus*, causes an illness marked by high fever, rash, and debilitating polyarthritis, which may persist for months. Though not typically fatal, the chronic joint pain significantly affects quality of life. The co-circulation of CHIKV and DENV in the same regions has also led to co-infections, complicating clinical diagnosis and management.

Herbal approaches using *Curcuma longa* (turmeric), *Tinospora cordifolia* (giloy), and Carica papaya leaf extract have shown potential in managing symptoms such as thrombocytopenia and inflammation.[11]

Ebola and Marburg viruses

Ebola virus and Marburg virus are highly virulent filoviruses responsible for causing viral hemorrhagic fevers (VHFs), diseases known for their severe and often fatal clinical manifestations. Human infections are typically initiated through direct contact with infected animals, such as fruit bats or non-human primates, and subsequently transmitted via contact with bodily fluids of infected persons. Ebola virus gained widespread notoriety during the 2014–2016 West Africa outbreak, which resulted in over 11,000 deaths and revealed serious gaps in regional and international outbreak response capacities. Symptoms begin with fever, fatigue, and muscle pain, progressing rapidly to vomiting, diarrhea, internal and external bleeding, and multi-organ failure. Marburg virus disease, though rarer, presents similarly and has mortality rates as high as 88% in some outbreaks.[12] Despite the development of Ebola vaccines (e.g., rVSV-ZEBOV) and investigational monoclonal antibodies, challenges persist in terms of access, infrastructure, and public trust. Herbal candidates with antiviral activity against filoviruses are being investigated, including phytochemicals that inhibit viral replication and modulate immune responses, although much of this work remains preclinical.

Avian and Swine Influenza viruses

Avian (H5N1, H7N9) and swine-origin influenza viruses (e.g., H1N1) are highly mutable, zoonotic strains of the *Orthomyxoviridae* family. These viruses have demonstrated the capacity for genetic reassortment, whereby human, avian, and swine influenza genes mix to form novel strains with pandemic potential. The 2009 H1N1 swine flu pandemic infected millions worldwide, particularly affecting younger age groups. Avian influenza remains of grave concern due to its high case fatality rate, despite limited human-to-human transmission. These strains often emerge in regions with intensive poultry farming, where humans and animals interact closely, creating an ideal environment for viral mutation and transmission.[13] Annual vaccination remains the cornerstone of influenza control; however, antigenic drift and shift necessitate constant reformulation. Antiviral drugs such as oseltamivir and zanamivir are available, but resistance has been documented. This has spurred renewed interest in natural inhibitors of neuraminidase or hemagglutinin, such as quercetin, resveratrol, and epigallocatechin gallate (EGCG) from green tea, which have shown inhibitory effects in various in vitro studies.[14]

Mechanism of antiviral action of medicinal plants

Herbal medicines have long been utilized in traditional systems of medicine to manage infectious diseases. Modern research has now begun to unravel the scientific basis behind the antiviral properties of many medicinal plants. Their bioactive constituents including alkaloids, flavonoids, terpenoids, glycosides, lignans and polyphenols that exhibit diverse mechanisms of action that target multiple stages of the viral life cycle.[15] This multitargeted approach makes herbal antivirals particularly valuable, as it reduces the likelihood of resistance development and enhances synergistic activity when used in combination with conventional therapies.

Inhibition of viral entry and attachment

One of the initial steps in viral infection is the attachment of the virus to host cell receptors, followed by entry into the cell via endocytosis or membrane fusion. Several plant-derived compounds have been shown to block this interaction, effectively preventing the virus from initiating infection. Glycyrrhizin (from *Glycyrrhiza glabra*, or licorice root) has demonstrated the ability to inhibit the entry of viruses such as SARS-CoV and HIV by interfering with viral envelope proteins. Epigallocatechin gallate (EGCG), a green tea catechin, can bind to viral surface glycoproteins and inhibit the fusion of viruses like influenza and hepatitis B virus (HBV). Quercetin, a flavonoid found in many fruits and vegetables, blocks viral entry by binding to surface receptors or interfering with viral proteins.[16]

Inhibition of viral replication and transcription

Once inside the host cell, viruses rely on the host machinery for replication. Many phytochemicals target viral polymerases, reverse transcriptases, or proteases, thereby disrupting the replication process. Andrographolide, the active component in *Andrographis paniculata*, has been shown to inhibit RNA synthesis in dengue virus and hepatitis C virus. Curcumin from *Curcuma longa* interferes with replication by modulating cellular signaling pathways (e.g., NF-κB, PI3K/Akt), which are often hijacked by viruses for replication. Baicalin, a flavonoid from *Scutellaria baicalensis*, inhibits the activity of viral RNA polymerase in influenza virus. [17]

Inhibition of viral protein synthesis and assembly

Disrupting the synthesis of viral structural proteins or their assembly into functional virions is another antiviral strategy adopted by plant-derived compounds. Berberine from *Berberis spp.* suppresses viral protein expression in herpes simplex virus (HSV) and inhibits capsid formation. Silymarin from *Silybum marianum* modulates the host's endoplasmic reticulum stress response, which affects the folding and processing of viral proteins in hepatitis C virus. [18,19]

Modulation of host immune response

A well-regulated immune response is essential to clear viral infections. Some herbal compounds act as immunomodulators, enhancing the body’s natural antiviral defenses without overstimulating inflammatory pathways. Withanolides in *Withania somnifera* (Ashwagandha) enhance natural killer (NK) cell activity and increase macrophage phagocytosis.[20] Polysaccharides from *Echinacea purpurea* and *Astragalus membranaceus* stimulate the production of interferons and cytokines involved in antiviral immunity. *Tinospora cordifolia* has shown immunomodulatory activity by balancing Th1/Th2 responses and stimulating leukocyte activity. [21]

Antioxidant and anti-inflammatory effects

Many viruses induce oxidative stress and inflammation, contributing to tissue damage and disease progression. Plant-based antioxidants help mitigate this damage and may indirectly reduce viral replication. Resveratrol from grapes and luteolin from celery and green peppers have both shown potent antioxidant and anti-inflammatory properties, beneficial in managing viral infections like respiratory syncytial virus (RSV) and influenza. *Azadirachta indica* (Neem)

extracts have demonstrated both antioxidant and direct antiviral effects against multiple RNA viruses.[22] Table 1 shows the mechanism of action of several herbal antivirals.

Table 1: Mechanisms of action of selected herbal antivirals.[23,24]

Plant/compound	Virus targeted	Mechanism of action
Glycyrrhizin (*Licorice*)	SARS-CoV, HIV	Inhibits viral entry and replication
Andrographolide	Dengue, HCV	Inhibits RNA synthesis and immune modulation
Curcumin (*Turmeric*)	Influenza, HIV	Modulates NF-κB pathway, anti-inflammatory
EGCG (*Green Tea*)	Influenza, HBV	Blocks viral attachment and entry
Quercetin	Multiple viruses	Inhibits entry, replication, antioxidant
Berberine	HSV	Inhibits protein synthesis and capsid assembly
Withanolides (*Ashwagandha*)	Influenza, SARS-CoV-2	Immunostimulant, antioxidant
Baicalin	Influenza	Inhibits RNA polymerase

Limitations of conventional antiviral therapies

Despite remarkable progress in virology and pharmacology, conventional antiviral therapies continue to face numerous limitations that compromise their long-term efficacy, safety, and accessibility. The increasing incidence of emerging and re-emerging viral diseases has exposed critical weaknesses in existing therapeutic approaches. The following are the major limitations associated with synthetic antiviral agents and vaccine-based strategies:

Narrow spectrum of activity

Most conventional antiviral drugs are designed to target specific viral enzymes or proteins, such as reverse transcriptase, proteases, or neuraminidase. While this high degree of specificity can enhance efficacy against the intended virus, it also significantly restricts the spectrum of antiviral activity. These agents often lack efficacy against genetically divergent strains or novel viruses. For example, drugs effective against herpesviruses are typically ineffective against RNA viruses like dengue or SARS-CoV-2. This single-target mechanism becomes a major drawback during outbreaks of new or mutated viruses that escape existing pharmacological interventions.[25]

Resistance development

One of the most pressing challenges in antiviral therapy is the rapid development of drug resistance. Viral pathogens, particularly RNA viruses such as influenza, HIV, and SARS-CoV-2, have high mutation rates, which allow them to quickly evolve resistance to specific drugs. For instance, prolonged use of oseltamivir (Tamiflu) has led to the emergence of resistant influenza strains, while acyclovir resistance has been documented in immunocompromised individuals

with recurrent herpesvirus infections.[26] This necessitates the continuous development of new antiviral molecules, which is both time-consuming and costly.

Adverse effects and toxicity

The use of synthetic antiviral drugs, particularly at high doses or over extended durations, is frequently associated with a wide range of adverse effects and systemic toxicities that can significantly compromise patient adherence and overall quality of life. Hepatotoxicity, or liver damage, is a well-documented side effect of drugs like ribavirin and nevirapine, while nephrotoxicity, affecting kidney function, has been reported with antivirals such as tenofovir.[27] Additionally, some agents, including efavirenz, have been linked to neuropsychiatric complications such as insomnia, dizziness, and even depression, which can be particularly debilitating. Gastrointestinal disturbances like nausea, vomiting, and diarrhea are also prevalent and can further reduce patient compliance. These adverse reactions are not only discomforting but can be life-threatening in vulnerable groups, including the elderly, pregnant women, children, and individuals with pre-existing health conditions or compromised immune systems. The systemic toxicity of these medications necessitates close monitoring and often limits their use, highlighting the urgent need for safer, better-tolerated antiviral alternatives such as those derived from medicinal plants, which generally exhibit lower toxicity and better biocompatibility.[28]

High cost and limited accessibility

The development and commercialization of modern antivirals, particularly biologics and monoclonal antibodies, involve complex, high-cost processes including advanced research, clinical trials, and regulatory approvals. As a result, many effective therapies remain financially inaccessible in low- and middle-income countries (LMICs). This disparity was starkly illustrated during the COVID-19 pandemic, where novel antivirals and vaccines were largely unavailable in poorer nations during early distribution phases. The high cost also limits stockpiling and widespread deployment during large-scale outbreaks or pandemics.[29]

Phytochemicals with antiviral activities

Phytochemicals, the naturally occurring bioactive compounds found in medicinal plants, play a crucial role in the therapeutic potential of herbal antivirals due to their diverse structural properties and multifaceted biological activities. These compounds exhibit significant antiviral effects by targeting various stages of the viral life cycle, ranging from viral entry and replication to assembly and release. Among them, flavonoids such as quercetin and kaempferol are widely studied for their ability to inhibit viral enzymes like reverse transcriptase and protease, thereby obstructing viral replication. Alkaloids, including berberine, have demonstrated efficacy in disrupting viral genome integration and inhibiting the transcription processes essential for viral proliferation. Terpenoids, such as glycyrrhizin from licorice root, are known to interfere with viral attachment and entry by modulating host cell receptors or viral envelope proteins.[30] Polyphenols, particularly epigallocatechin gallate (EGCG) from green tea, offer both immunomodulatory and potent antioxidant properties, which not only suppress viral propagation but also mitigate virus-induced oxidative stress and inflammation. Saponins, another important group, are recognized for their ability to stimulate the host immune response and directly inhibit

viral replication through membrane disruption and interference with viral protein synthesis. Together, these phytochemicals exhibit a broad-spectrum antiviral potential and offer synergistic effects when used in combination, making them promising candidates for the development of safer, more effective antiviral therapies derived from natural sources.[24]

Novel drug delivery approaches for herbal antivirals

While herbal antivirals hold immense promise due to their broad-spectrum activity and natural origin, their clinical application is often hindered by critical pharmacokinetic limitations. Many bioactive phytochemicals suffer from poor water solubility, chemical instability, rapid metabolism, and low bioavailability, which significantly reduce their therapeutic efficacy when administered in conventional forms. To address these challenges, recent advances in pharmaceutical technology have led to the development of novel drug delivery systems tailored specifically for herbal compounds. These innovative approaches aim to enhance the stability, absorption, targeted delivery, and sustained release of phytochemicals, thereby maximizing their antiviral potential. [31,32]

Nanoparticles

Nanotechnology has emerged as a powerful tool in the delivery of herbal antivirals. Polymeric, lipid-based, and metallic nanoparticles can encapsulate plant-derived compounds, improving their aqueous solubility and enabling controlled and targeted drug release. For instance, curcumin-loaded polymeric nanoparticles have demonstrated enhanced antiviral and anti-inflammatory activity against influenza virus in preclinical studies compared to free curcumin. These nanoformulations help protect sensitive compounds from degradation in the gastrointestinal tract and enable targeted delivery to infected tissues, thereby reducing required doses and minimizing systemic side effects.[33]

Liposomes and phytosomes

Liposomes, spherical vesicles composed of phospholipid bilayers, are widely used to encapsulate both hydrophilic and lipophilic herbal constituents. They enhance cellular uptake and provide protection against enzymatic degradation. A specialized variant, phytosomes, involves binding phytochemicals with phospholipids to improve membrane permeability and bioavailability. This approach has been effectively applied to enhance the delivery of poorly absorbable compounds like quercetin and silymarin, resulting in improved antiviral efficacy. [34]

Hydrogels and transdermal patches

For localized viral infections, especially those affecting the skin or mucosal surfaces (e.g., herpes simplex virus), hydrogels and transdermal patches offer a promising method of topical delivery. These systems provide sustained and site-specific release, improve patient compliance, and minimize systemic exposure. Hydrogels can be loaded with herbal extracts or nanoparticles and applied directly to affected areas, where they maintain moisture and facilitate prolonged drug action.[35]

Solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers (NLCs)

SLNs and NLCs are advanced lipid-based delivery platforms that are particularly suitable for encapsulating lipophilic herbal compounds like terpenoids and flavonoids. They offer

excellent biocompatibility, enhanced solubility, and controlled release while protecting sensitive phytochemicals from hydrolytic and oxidative degradation. These systems are being investigated for delivering herbal antivirals for both systemic and topical applications, with promising results in viral infections such as hepatitis, herpes, and influenza. [36]

Safety, toxicity and regulatory perspectives

Although herbal antivirals are generally considered safe due to their natural origin and long-standing use in traditional medicine, their safety profile cannot be universally assumed, and several concerns warrant careful evaluation. Toxicity and overdose are important considerations, as excessive or prolonged consumption of certain herbs can lead to adverse effects. For instance, *Glycyrrhiza glabra* (licorice root), while possessing antiviral properties, can cause hypertension, hypokalemia, and hepatotoxicity when consumed in high doses or over extended periods. Additionally, herb-drug interactions present a significant risk, particularly in patients undergoing conventional antiviral or immunosuppressive therapy.[37,38] Herbal constituents can modulate cytochrome P450 enzymes or P-glycoprotein activity, thereby altering the absorption, distribution, metabolism, and excretion (ADME) of co-administered pharmaceutical agents, leading to reduced efficacy or increased toxicity. A major barrier to the consistent clinical use of herbal antivirals is the lack of standardization in herbal formulations; variations in plant species, harvesting methods, extraction processes, and storage conditions can result in fluctuating phytochemical concentrations, leading to inconsistent therapeutic outcomes and safety profiles. Furthermore, the regulatory landscape for herbal medicines remains fragmented, with significant variability across countries. Unlike synthetic drugs, herbal products often bypass rigorous clinical testing, leading to challenges in establishing evidence-based efficacy and safety. Recognizing this gap, regulatory bodies such as the World Health Organization (WHO), AYUSH (India), U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA) are actively working to establish comprehensive guidelines and frameworks. These include criteria for identity, purity, potency, and clinical validation, aimed at ensuring quality assurance and patient safety. Harmonizing global regulatory standards and promoting phytochemical standardization will be essential to fully realize the therapeutic potential of herbal antivirals within modern medical systems. [39,40]

Conclusion:

In a time increasingly challenged by the frequent emergence and re-emergence of viral infections such as COVID-19, dengue, Zika, and Ebola, the demand for effective, safe, and affordable antiviral solutions has become more pressing than ever. Herbal antivirals present a natural, accessible, and comprehensive therapeutic option. They are grounded in centuries of traditional medical practices and are now being supported by growing scientific evidence. The diverse array of phytochemicals found in medicinal plants, including flavonoids, alkaloids, terpenoids, and polyphenols, demonstrate broad-spectrum antiviral activity. These compounds act at different stages of the viral life cycle and also help in modulating the host's immune response. Additionally, herbal treatments tend to have fewer side effects and greater tolerability compared to many synthetic antiviral drugs, making them especially suitable for prolonged use

and for populations with higher vulnerability. However, several significant challenges remain before herbal antivirals can be fully integrated into mainstream healthcare systems. These include the absence of standardized formulations, inconsistent phytochemical content, limited clinical trials, and a lack of clear global regulatory guidelines. To address these concerns, there is a need for comprehensive scientific evaluation, consistent toxicological assessment, and internationally recognized regulatory protocols. The application of advanced drug delivery technologies can also improve the bioavailability and therapeutic outcomes of plant-based antivirals. Furthermore, the implementation of rigorous standardization practices and well-designed clinical studies is essential for establishing the credibility and acceptance of these therapies.

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MEDICINAL POTENTIAL OF HERBAL PLANTS IN UTERINE FIBROIDS

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Abstract:

Uterine fibroids, or leiomyomas, are the most associated benign tumors in women of reproductive age and can cause a range of symptoms, comprising heavy menstrual bleeding, pelvic pain, and infertility. While conventional medical treatments like surgery and pharmacotherapy are commonly employed, these methods can have significant side effects, leading many patients to seek alternative or complementary therapies. Herbal plants' ability to control hormones, lower inflammation, and stop fibroid growth has made them attractive options for treating uterine fibroids. This chapter explores the medicinal potential of various herbal plants, including Vitex agnus-castus (Chaste Tree)**,** Curcuma longa (Turmeric)**,** *Withania somnifera* (Ashwagandha)**,** *Glycyrrhiza glabra* (Licorice)**,** and others. Bioactive substances found in these plants may help enhance uterine health, relieve fibroid symptoms, and restore hormonal balance. The chapter discusses the mechanisms of action, key compounds, and therapeutic benefits of these herbs, along with the clinical evidence supporting their use. It also addresses safety concerns and provides recommendations for incorporating herbal therapies into fibroid management. Although encouraging, more investigation and clinical testing are required to validate the effectiveness and safety of these herbal treatments for uterine fibroids.

Keywords: Uterine Fibroids, Alternative Therapy, Herbal Medicine, Fibroid Management

Introduction:

Leiomyomas, another name for uterine fibroids, are non-cancerous growths that form in the uterus' muscular wall. One of the most prevalent gynecological disorders in the world, fibroids are thought to affect 70–80% of women by the age of 50. From microscopic to bigger masses, these tumors can cause serious symptoms like infertility, pelvic pain, heavy menstrual flow, and frequent urination. Although most fibroids are asymptomatic, their impact on a woman’s quality of life can be profound, leading many to seek medical treatment. Conventional management often involves medications aimed at reducing symptoms, such as hormonal therapies, and surgical options like myomectomy or hysterectomy. But these medicines might have risks and adverse effects, which is why many are looking for complementary or alternative therapy.[1-3]

The use of herbal medicine as a possible treatment for uterine fibroids has drawn more attention in recent years. Many herbal plants are now being acknowledged for their medicinal

qualities in contemporary clinical settings, after centuries of use in traditional medicine. These plants offer a wide range of bioactive compounds with the potential to modulate hormonal imbalances, reduce inflammation, and inhibit the growth of fibroids. Notably, many uterine fibroids are estrogen-dependent, making hormonal regulation a key target in herbal treatment. Herbs such as Vitex agnus-castus (Chaste Tree), Curcuma longa (Turmeric), *Withania somnifera* (Ashwagandha), and *Glycyrrhiza glabra* (Licorice) have shown promising effects in balancing estrogen and progesterone levels, which may help in reducing the size of fibroids and alleviating their symptoms.[4-6]

Overview of uterine fibroids

These benign growths are among the most common gynecological conditions affecting women, particularly those of reproductive age. It is estimated that up to 70-80% of women may develop fibroids by the time they reach 50 years old, though many women with fibroids remain asymptomatic and unaware of their presence. Fibroids can vary greatly in size, from microscopic growths to large masses that can distort the uterus. They can also be located in various parts of the uterus, including the submucosal**,** intramural**,** and subserosal regions, each affecting different aspects of reproductive health.

1. Types of uterine fibroids

Fibroids are classified based on their location within the uterus.[7,8]

- **Intramural Fibroids**: These fibroids are the most prevalent kind and are found inside the uterine wall's muscles. They can cause the uterus to become enlarged, leading to pelvic pressure and other symptoms.
- **Submucosal fibroids**: These fibroids grow just beneath the inner lining of the uterus (the endometrium). They are the most likely type to cause abnormal bleeding and infertility, as they may interfere with the uterine lining's ability to properly nurture an embryo.
- **Subserosal fibroids**: Located on the outer layer of the uterus, these fibroids can sometimes grow large enough to cause significant pressure on surrounding organs, leading to symptoms such as frequent urination or constipation.
- **Pedunculated fibroids**: These fibroids are attached to the uterus by a stalk, and they can either be submucosal or subserosal. They may twist, causing pain and other complications.

2. Causes and risk factors

While the exact cause of uterine fibroids is not entirely understood, several factors are believed to contribute to their development:

- **Hormonal imbalance**: Fibroids are estrogen-dependent tumors, meaning that they tend to grow in response to estrogen and progesterone, the primary female reproductive hormones. This is why fibroids are more common during the reproductive years and shrink after menopause when hormone levels decrease.

- **Genetic factors**: A family history of uterine fibroids can increase the likelihood of developing them, suggesting a genetic predisposition to their formation.
- **Age and ethnicity**: Fibroids are more common in women aged 30 to 40, and African American women are at higher risk of developing fibroids, often at an earlier age and with more severe symptoms.
- **Obesity and lifestyle**: Higher body fat levels are linked to increased estrogen production, and women who are overweight may have a higher risk of fibroid development.
- **Environmental and dietary factors**: Certain environmental and dietary factors, such as high red meat consumption and low intake of fruits and vegetables, have been associated with an increased risk of fibroids.

3. **Symptoms of uterine fibroid**

While many women with fibroids experience no symptoms, those who do may suffer from a variety of discomforts, including:

- **Heavy menstrual bleeding**: One of the most common symptoms, characterized by prolonged periods or excessive blood flow (menorrhagia).
- **Pelvic pain and pressure**: Large fibroids can put pressure on the bladder, rectum, or other organs, causing pain, discomfort, and urinary or bowel issues.
- **Frequent urination**: Fibroids, especially subserosal ones, may put pressure on the bladder, leading to frequent or urgent need to urinate.
- **Painful intercourse**: Fibroids can cause pelvic pain during or after sexual activity.
- **Reproductive issues**: In some cases, fibroids can interfere with fertility, cause miscarriage, or complicate pregnancy.
- **Back or leg pain**: Large fibroids may cause pain or discomfort in the lower back or legs due to pressure on nearby muscles or nerves.

4. Diagnosis of uterine fibroids

The diagnosis of uterine fibroids typically involves a combination of the following:

- **Pelvic examination**: A physician may detect an enlarged uterus or unusual lumps during a pelvic exam.
- **Ultrasound**: The most common imaging technique used to confirm the presence, size, and location of fibroids.
- **MRI (Magnetic Resonance Imaging)**: An MRI may be used to provide more detailed images of the fibroids and help plan treatment, especially in cases of larger or more complicated fibroids.
- **Hysteroscopy**: This procedure involves inserting a thin, flexible tube with a camera through the cervix to view the inside of the uterus and directly examine fibroids.
- **Sonohysterography**: An ultrasound technique combined with a saline injection into the uterus to get clearer images of submucosal fibroids.

5. Treatment options

Depending on the patient's reproductive objectives and the severity of the symptoms, there are several treatment options for uterine fibroids.[9-11]

- **Medications**: Hormonal treatments such as birth control pills **or** progestin-releasing intrauterine devices (IUDs) can help control symptoms like heavy bleeding. Medications that suppress estrogen production, such as GnRH agonists, may shrink fibroids temporarily.
- **Surgical options**: For severe cases, surgical treatments such as myomectomy (removal of the fibroids) or hysterectomy (removal of the uterus) may be necessary.
- **Non-invasive procedures**: Techniques like uterine artery embolization (UAE)**,** which blocks blood supply to the fibroids, and MRI-guided focused ultrasound (MRI-FU) are minimally invasive options for reducing fibroid size.
- **Alternative therapies**: Increasingly, women are turning to alternative and complementary treatments, including herbal remedies and dietary changes, to manage symptoms or shrink fibroids naturally.

Conventional treatment options for uterine fibroids

Even though they are usually benign, uterine fibroids can have serious side effects, such as irregular menstruation, pelvic pain, and issues with fertility. When these symptoms affect a woman's quality of life or pose a threat to her reproductive health, conventional treatment options are often considered. These treatments range from medications to surgical interventions, and the choice of treatment depends on factors such as the size and location of the fibroids, the severity of symptoms, the woman’s age, and her desire to maintain fertility.

Here is an overview of the conventional treatment options for uterine fibroids:

1. Medications

Several medications are used to manage symptoms associated with uterine fibroids or to shrink the fibroids before surgery. These include hormonal treatments, non-hormonal medications, and drugs that help manage pain and bleeding.

2. Minimally invasive procedures

For women who need treatment but wish to avoid major surgery, minimally invasive procedures are increasingly being used. These techniques are typically done on an outpatient basis with a shorter recovery time than traditional surgery.

a. Uterine Artery Embolization (UAE)

b. MRI-Guided Focused Ultrasound (MRgFUS)

c. Endometrial ablation

3. Surgical options

Surgery may be required for women with larger or more symptomatic fibroids or when no other treatment works. Surgical options vary depending on the severity of the condition and the woman’s reproductive goals.

a. Myomectomy

b. Hysterectomy

4. Alternative and adjunctive treatments

In addition to the conventional treatments mentioned above, some women with uterine fibroids explore alternative therapies or use them as adjuncts to their primary treatment. These may include:

- **Acupuncture**: Used to manage pain and regulate menstrual cycles.
- **Herbal remedies**: Certain herbs are thought to help balance hormones and reduce fibroid symptoms, though scientific evidence is still limited.
- **Dietary modifications**: A diet high in fruits, vegetables, and antioxidants and low in red meat may help reduce the risk of fibroids or manage symptoms.

  While alternative therapies can be beneficial in symptom management, they are typically considered complementary to traditional medical interventions.

Key medicinal plants for uterine fibroids

In recent years, herbal therapy has drawn a lot of interest as a natural treatment for uterine fibroids. Numerous medicinal herbs have demonstrated promise in reducing the symptoms of uterine fibroids, including hormonal imbalances, pelvic pain, and excessive menstrual flow. Some plants contain bioactive compounds that may influence hormonal regulation**,** reduce inflammation, or shrink fibroid growth. While scientific research on the effectiveness of these herbs specifically for uterine fibroids is still ongoing, traditional use and preliminary studies suggest that they may offer therapeutic benefits.

Here, we highlight several key medicinal plants that have been studied or traditionally used for uterine fibroids.[12-17]

1. *Vitex agnus-castus* (chaste tree)

Vitex agnus-castus, commonly known as chaste tree, is a well-known herb in traditional medicine for regulating hormonal imbalances, particularly those related to the menstrual cycle. It has been used in Traditional Chinese Medicine (TCM) and Western herbalism to address conditions like irregular periods, premenstrual syndrome (PMS), and menstrual disorders.

Mechanism of action:

- **Hormonal modulation**: Vitex works by influencing the pituitary gland, leading to an increase in progesterone and a reduction in estrogen**.** This balance may help alleviate conditions like uterine fibroids, which are often sensitive to estrogen.
- **Anti-inflammatory effects**: The herb has mild anti-inflammatory properties that may reduce pelvic discomfort caused by fibroids.

Potential benefits for uterine fibroids:

- Reduces heavy menstrual bleeding and painful periods.
- May help balance hormonal levels, particularly in women with estrogen dominance.
- Could promote a normal menstrual cycle and potentially prevent fibroid growth.

2. Green tea (*Camellia sinensis*)

Green tea is widely known for its antioxidant and anti-inflammatory properties. It contains polyphenols, particularly epigallocatechin gallate (EGCG), which have been studied for their potential health benefits. In the case of uterine fibroids, green tea has gained attention due to its ability to reduce oxidative stress and modulate estrogen levels.

Mechanism of action:

- **Antioxidant effects**: The polyphenols in green tea, especially EGCG, help reduce **oxidative stress**, a factor believed to contribute to fibroid development and growth.
- **Estrogen modulation**: Green tea may help modulate estrogen metabolism, which is essential in managing estrogen-driven conditions like fibroids.

Potential benefits for uterine fibroids:

- May inhibit fibroid growth by reducing oxidative damage and inflammation.
- May help reduce the size of fibroids over time by affecting estrogen receptors.
- Could help alleviate symptoms like heavy bleeding associated with fibroids.

3. Turmeric (*Curcuma longa*)

Turmeric, particularly the active compound curcumin, has long been used in Ayurvedic and traditional medicine for its anti-inflammatory**,** antioxidant, and anti-cancer properties. It is commonly consumed as a spice or in supplement form.

Mechanism of action:

- **Anti-inflammatory and antioxidant properties**: Curcumin in turmeric has potent anti-inflammatory and antioxidant properties that may help reduce the inflammation and oxidative stress associated with uterine fibroids.
- **Regulation of estrogen**: Some studies suggest that curcumin may affect estrogen metabolism, which can influence the growth of estrogen-sensitive fibroids.

Potential benefits for uterine fibroids:

- Reduces inflammation and pelvic pain.
- May help shrink fibroids by reducing inflammation and promoting a more balanced hormonal environment.
- May alleviate heavy bleeding by regulating the estrogen pathway.

4. Dong Quai (*Angelica sinensis*)

Dong Quai, also known as female ginseng, is a key herb in Traditional Chinese Medicine (TCM), used for women's reproductive health. It is commonly employed to regulate menstrual cycles, ease menstrual cramps, and improve blood circulation.

Mechanism of action:

- **Hormonal balance**: Dong Quai is believed to regulate the hormonal system, particularly estrogen levels, which may help manage fibroids that are estrogen-sensitive.
- **Blood circulation**: Dong Quai is also known to improve blood circulation and may help reduce heavy bleeding by promoting healthy uterine function.

Potential benefits for uterine fibroids:

- May help regulate menstrual cycles and reduce the heavy bleeding associated with fibroids.
- Improves blood circulation, potentially reducing pelvic congestion and pain.
- May help balance hormones, reducing the symptoms of estrogen dominance.

5. Milk thistle (*Silybum marianum*)

Milk thistle is an herb known for **its** liver-protective effects, particularly through its active compound silymarin. It has been traditionally used to detoxify the liver, improve liver function, and promote overall health.

Mechanism of action:

- **Liver detoxification**: By supporting the liver's detoxification processes, milk thistle may help regulate estrogen levels, as the liver is responsible for metabolizing estrogen.
- **Anti-inflammatory effects**: Milk thistle has strong anti-inflammatory properties, which can help alleviate pelvic pain and reduce the inflammation associated with fibroids.

Potential benefits for uterine fibroids:

- Supports liver health, enhancing the liver's ability to process and detoxify estrogen.
- May help balance estrogen levels in the body, which is particularly beneficial for women with estrogen-sensitive fibroids.
- Could reduce the symptoms of fibroid-related pain and heavy menstrual bleeding.

6. Black cohosh (*Actaea racemosa*)

Black cohosh is another herb that has been traditionally used to address various women's health issues, including menopausal symptoms, PMS, and hormonal imbalances. It is commonly used in both Western herbalism and Ayurvedic medicine.

Mechanism of action:

- **Hormonal balance**: Black cohosh contains compounds that have estrogen-like effects, which may help balance estrogen levels in women with fibroids.
- **Anti-inflammatory effects**: It also has anti-inflammatory properties, which can alleviate symptoms like pelvic pain and inflammation.

Potential benefits for uterine fibroids:

- Balances estrogen levels**,** which can help reduce the symptoms of fibroids, especially in women with estrogen dominance.
- May help reduce pelvic pain and cramping associated with fibroids.
- Could provide relief from menopausal symptoms in women who are approaching menopause and have fibroids.

7. Red clover (*Trifolium pratense*)

Red clover is rich in isoflavones, which are plant-based compounds that have estrogen-like effects. It has been used traditionally to treat various women's health issues, including hot flashes**,** menstrual irregularities, and osteoporosis**.**

Mechanism of action:

- **Isoflavones and estrogenic effects**: The isoflavones in red clover can bind to estrogen receptors in the body, potentially helping to regulate estrogen levels and reduce fibroid growth in estrogen-sensitive tissue.
- **Anti-inflammatory and antioxidant properties**: Red clover also possesses antioxidant properties that help reduce oxidative stress and inflammation, which may aid in fibroid management.

Potential benefits for uterine fibroids:

- May help regulate estrogen levels, reducing symptoms of estrogen dominance associated with fibroids.
- Reduces inflammation and oxidative stress, potentially limiting fibroid growth and reducing symptoms.
- Could offer relief from menstrual irregularities and heavy bleeding.

Numerous potential treatments for uterine fibroids are available through herbal therapy, especially for the management of symptoms like hormonal imbalances, pelvic pain, and excessive menstrual flow. Key medicinal plants such as Vitex Agnus-Castus, Turmeric, Dong Quai, and Green Tea provide a natural alternative to conventional treatments, often with fewer side effects. However, it's important to remember that while herbal remedies can be beneficial, they should be used with caution and under the guidance of a healthcare provider, especially when combined with other treatments or medications. Further clinical studies are needed to fully understand the efficacy and safety of these herbs for fibroid management, but they hold promise as part of a holistic approach to treating uterine fibroids.

Integrating herbal medicine with conventional treatment for uterine fibroids

The treatment of uterine fibroids typically involves a combination of approaches, depending on the size, location, symptoms, and individual health considerations. Conventional treatments for uterine fibroids often include pharmacological therapies, hormonal therapies, and surgical options. On the other hand, herbal medicine offers a more natural, holistic approach, focusing on symptom management and hormonal balance. Integrating herbal medicine with conventional treatment can provide a comprehensive, multi-faceted approach to uterine fibroid management.

Benefits of integrating herbal medicine with conventional treatments

Integrating herbal medicine with conventional treatments for uterine fibroids may offer several complementary benefits, including.[18-22]

a. Hormonal regulation

Many uterine fibroids are estrogen-dependent, meaning that their growth is influenced by hormonal imbalances, particularly excess estrogen. Herbal remedies, such as Vitex Agnus-Castus, Turmeric, and Green Tea, can help balance hormonal levels, reducing estrogen dominance and potentially preventing the growth of fibroids. When combined with hormonal

therapies (e.g., birth control pills, GnRH agonists), herbal medicine may help optimize the treatment's effectiveness while mitigating side effects.

b. Symptom management

Herbal medicine offers natural ways to manage the symptoms of uterine fibroids, such as pelvic pain**,** heavy menstrual bleeding, and fatigue. For example, Dong Quai may help regulate menstrual cycles and reduce cramping, while Black Cohosh can alleviate menopausal-like symptoms in women approaching menopause with fibroids. Herbs such as Turmeric and Milk Thistle may also reduce inflammation and pain, supporting the body's healing process during pharmacological treatments.

c. Reducing side effects of conventional medications

Many conventional treatments for uterine fibroids, especially hormonal therapies, come with side effects like weight gain, mood swings, and reduced libido. Herbal remedies may help counteract these adverse effects. For example, Ashwagandha can support adrenal health and reduce **stress** caused by hormonal treatments, while Red Clover can mitigate some of the side effects associated with hormone therapy.

d. Improving overall reproductive health

Herbal remedies can also support general reproductive health, improving uterine tone, blood circulation, and overall vitality. Herbs like Dong Quai**,** Ginseng, and Red Clover have been traditionally used to promote uterine health and fertility, which can be particularly beneficial for women seeking to maintain reproductive function.

Conclusion:

Combining herbal medicine with traditional uterine fibroids treatments can provide a comprehensive strategy that treats the fibroids' symptoms as well as their underlying causes. Herbal medicines are a viable addition to conventional medical therapies since they offer natural support for pain management, hormone regulation, and general reproductive health. However, careful consideration of safety**,** potential herb-drug interactions, and the individualized nature of treatment is essential for maximizing the benefits of this integrative approach. Women considering herbal treatments for uterine fibroids should consult with qualified healthcare providers, including those with expertise in both conventional medicine and herbal therapy**,** to develop a personalized, safe, and effective treatment plan. Through collaboration and careful monitoring, herbal medicine can complement conventional treatments to provide a more comprehensive, well-rounded approach to uterine fibroid management.

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BERBERINE AS FUTURE THERAPEUTIC AGENT: A HIGHLIGHT

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Abstract:

The modern journey of discovering and developing new drugs is both thrilling and demanding. To streamline and enhance the success of new product discovery and development, natural products, which are evolutionarily refined as drug-like molecules, have attracted significant attention as promising sources of new chemical entities. Herbal medicines play a vital role in maintaining and restoring health, thereby contributing to an improved quality of life in humans. Alkaloids, a group of naturally occurring organic compounds, have long been a focal point in natural products chemistry due to their diverse chemical structures and remarkable biological activities. Historically, plants containing berberine have been widely utilized in various traditional phytotherapies. In numerous traditional medicinal plants berberine a significant alkaloid, is found. In recent years, berberine has garnered significant attention for its promising potential in treating metabolic as well as other long-lasting diseases. Berberine a potential phytochemical is an alkaloid found in many medicinal plant species and have been used since prehistoric times for the treatment of varied disorders. In this study we have highlight the pharmacological effects of berberine considering it a future therapeutic agent as it is possessing multiple therapeutic effects.

Keywords: Alkaloids, Berberine, *Berberis aristata*, Phytochemical.

Introduction:

Throughout history, humans have count on natural sources to meet their elementary requirements, providing resources such as accommodation, medicines, fragrances, nourishment, wear, flavours, fertilizers, and means of conveyance. For a significant portion of the global population, medicinal plants remain a cornerstone of healthcare systems, particularly in underdeveloped countries, wherever medicines from herbal origin have a longstanding tradition of usage. The recognition and advancement of the medicinal as well as financial aids of these medicinal herbs are increasing in both developed & underdeveloped countries. Plants have served as the basis for traditional medicinal systems that have existed for thousands of years. Plants endure to deliver humanity by means of novel medicines. While few of the ascribed benefits of florae have been recognized inaccurate, treatments using medicinal plants are founded on experimental knowledge accumulated over historical periods. The earliest archives, inscribed on tablets of clay in wedge-shaped around two thousand six hundred BC in Mesopotamia, mention the usage of constituents like oil of *Glycyrrhiza glabra* oil and juice of

Papaver somniferum. These remedies are still utilized today to treat illnesses extending from colds & coughs to inflammatory diseases & infections of parasites. [1,2]

India possesses a wealth of well-documented and extensively practiced traditional herbal medicine. As one of the twelve mega biodiversity centres, the country is home to over forty-five thousand plant species. India's unparalleled biodiversity is attributed to its sixteen distinct agro-climatic zones, more than ten zones of vegetation, and approximately fifteen provinces of biotics. India's selected zone of economic in the ocean, covering an area equivalent to three-quarters of its land, hosts a rich diversity of plants, several of which possess healing potential. Ancient texts reference approximately 1,500 plants with medicinal uses, of which around 800 have been utilized in traditional medicine. The World Health Organization has recently defined traditional medicine (including herbal drugs) as therapeutic practices that have existed for centuries, predating the expansion and widespread use of medicine of modern origin, and continue to be practiced today. Medicines specifically of traditional background is the culmination of curative knowledge passed down through generations of practitioners within indigenous systems of medicine. Herbal drugs refer to traditional medicines that primarily rely on preparations made from medicinal plants for treatment. The traditional Indian manuscripts of comprise the Atharvaveda & Charak Samhita as well as Rigveda & Sushruta Samhita. As a result, medicines from herbal and traditional remedies have been developed from the amusing ethnicities of ancient cultures and scientific legacy. Medicines from herbs are naturally occurring substances derived from plants, cast-off for dealing ailments within home-grown & regional traditions of healing. These products consist of complex mixtures of organic compounds, which can be sourced from any raw or processed part of a plant. Herbal medicine is deeply embedded in cultures across the globe. While there are various systems of traditional medicine, each shaped by social conditions, environment, and geography, all these systems share a common belief in a holistic approach to life. [2, 3, 4]

A long-standing custom of medicines from herbal resources is practiced in India, as demonstrated by Ayurveda, a practice that has endured for over two thousand years, supported by a robust scientific footing. Ayurveda, the meaning of which factually known as the information “Veda of life” i.e. Ayur, originated in the Atharvaveda (approx. 1500 to 1000 BC) & has been practiced for thousands of years, grounded in scientific principles.[5]

Phytochemicals: The term "phytochemical" comes from the Greek word "phyto," which means plants. Phytochemicals are secondary metabolites generally having low molecular-weight naturally occurring in plants. These biologically active molecules are crucial in normal cellular metabolism and contribute to health promotion and disease prevention. The distinction between primary and secondary metabolites is that primary metabolites are involved in energy metabolism and the structure of plant cells, whereas secondary metabolites are non-nutritive dietary compounds that play a key role in plant-environment interactions, protecting plants from insects as well as fungi. The composition of food plays a crucial role in human health and aging. Research has shown that the quantity and quality of nutrients we consume each day are essential

in influencing health outcomes and disease conditions. In a typical human diet, more than 1.4 gram of phytochemicals are consumed daily, while vegans and vegetarians may ingest significantly higher amounts of secondary metabolites. However, there are no established recommended intake levels for phytochemicals. A huge class of phytochemicals play a crucial role in the treatment of various diseases. The world is rich in plants such as fruits, leaves and roots as well as spices & vegetables and with over eighty percent of their chemical configurations and contents still undiscovered. Hence, there is a growing interest in exploring these phytochemicals as alternative drug sources that are safer, have fewer side effects, and are relatively more affordable. Different plant species contain a variety of phytochemicals that can be used to treat numerous ailments. [6, 7]

Alkaloids: Alkaloids are among the most diverse groups of secondary metabolites in nature, and their discovery has had a significant impact on the fields of pharmacology and natural products chemistry. These nitrogen-containing compounds are recognized for their powerful biological activities, which can vary from therapeutic benefits to toxic effects. Alkaloids, sourced from various organisms such as plants, fungi, and marine species, have been traditionally used in medicine and continue to inspire modern drug discovery. In natural products chemistry, alkaloids hold great importance because of their structural complexity and diverse pharmacological activities. Alkaloids have gained significant attention for their role in plant defence mechanisms and their applications in clinical settings, owing to their ability to influence biological pathways. Currently, more than 5000 alkaloids are known. The term "alkaloids" originates from "alkaline" and was initially used to refer to any nitrogen-containing base. Alkaloids are typically organic bases that form salts with acids and, when soluble, produce alkaline solutions. Alkaloids primarily function in plant defence against herbivores and pathogens. Research indicates that approximately 20% of plant species contain alkaloids. Many alkaloids have been used in medicine for centuries and remain a significant component of modern drug formulations. In ancient times, people used plant extracts containing alkaloids to treat a wide range of ailments, including bite of snakes, fever, and mental disorders. Isolated, pure plant alkaloids and their synthetic derivatives are widely used as essential medicinal agents worldwide due to their pain & spasm relieving and bactericidal properties. Certain alkaloids are used as antiseptics because of their antibiotic properties, such as berberine in ophthalmic treatments and sanguinarine in dental pastes. [8, 9, 10]

***Berberis aristata* (BA):** In the prehistoric era, various plants were used for their medicinal properties. Evidence of herbal plants being used as a source of medicine can be found in different cultures, such as those of Indian vaids. Since ancient times, India’s indigenous medicinal system has incorporated herbal plants as a traditional source of medicine, as the country is recognized as a rich reservoir of medicinal plants. One of them is BA, was first described by AL Jussieu in the year 1789. [11,12]

BA Commonly referred to as Indian barberry, this is a species of flowering shrub native to the Himalayan part of India. It is found extensively in India & Nepal as well as Bhutan and in

some parts of Sri Lanka, also in several southern part of Asia. It is an ageless bush belonging to the Berberidaceae family. In figure 1, the taxonomical classification of BA is showed. It is a minor, evergreen, bushy plant that can reach a height of up to 4 meters. It is commonly known as Indian barberry, Chitra & Daru Haldi as well as some people called it as Daruharidra & Tree turmeric. The bark of the plant is covered with thorns, and it has 5-8 leaf tufts with a pinnated venation. The upper superficial part of the leaves is shady green, while the lower surface is lighter in colour. In India, the stem and root parts of the BA plant are sold under the name Daruharidra. In several communities *BA* is used as a traditional medicine In the communities named Bhotiya of the Himalayan regions of India, the root decoction of BA is used to treat eye ailments. Traditionally, the aqueous as well as methanolic extract of BA has shown promise in treating osteoporosis, pain of joints, and symptoms of menopause. In certain rural areas of India, polyherbal medicines containing BA are used to treat piles. In the communities such as Malani tribal specifically of Himachal Pradesh, BA is cast-off to treat conditions like malaria & skin diseases. The juices of the leaf and fruit are said to have efficacy against diarrhoea and dysentery, while a root decoction is cast-off to treat jaundice. [13,14,15]

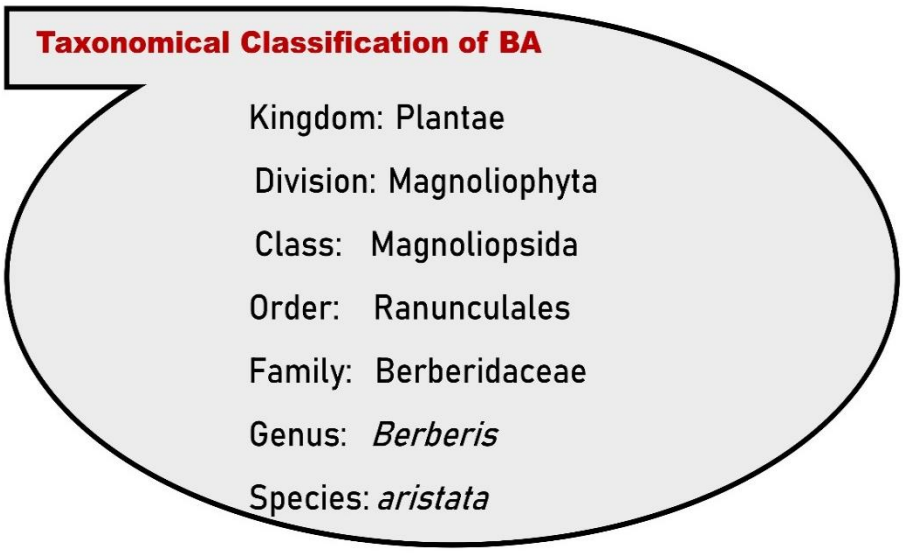

Figure 1: Taxonomical classification of BA. [14]

Berberine: It is a natural alkaloid compound present in several medicinal plants of the Berberidaceae family. *Berberis* species, including *Berberis aristate* & *Coptis trifolia,* as well as *Mahonia bealei & Hydrastis canadensis*, have attracted considerable interest in recent years for their wide-ranging pharmacological effects and therapeutic potential. Berberine is a yellow bioactive compound that can be derived from various plant species. Berberine is typically located in the roots and rhizomes of *Berberis* species and is extracted using various techniques for traditional medicine and pharmaceutical purposes. The berberine content varies based on the plant species, geographical origin, and conditions of growth, while the extraction and refinement methods significantly impact the quality of berberine used in research and medicine. In the era of pharmaceutical products and nutraceuticals, this powerful alkaloid has drawn global attention from researchers and scientists, leading to extensive studies on its diverse pharmacological

effects and potential uses in treating various diseases. Berberine is classified as an alkaloid, a group of compounds primarily composed of basic substances of nitrogen-content. Its molecular formula is $C_{40}H_{18}NO_4$ & it has a molecular weight of 336.337 g/mol. Berberine has been used for centuries in traditional Chinese and Indian medicine to address a variety of health conditions. Berberine is an important molecule in pharmacology as well as medicinal chemistry and contains nonbasic quaternary benzylisoquinoline alkaloid. In the figure 2 chemical structure of berberine is presented. [16, 17, 18, 19]

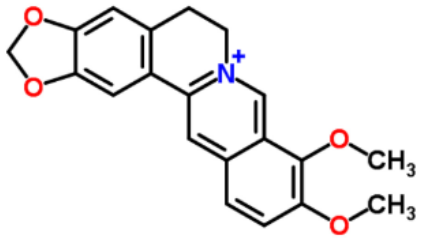

Figure 2: Structure of Berberine [19]

Pharmacological activities of berberine

Antioxidant activity

Beneath the usual conditions, the body sustains a balance between antioxidants & pro-oxidants, such as reactive oxygen and nitrogen species (ROS & RNS). In the excessive oxidative stress condition, there is an imbalance between pro-oxidants and antioxidants happens. Oxidative stress accumulates through various mechanisms, including an increase in the generation of species which are reactive in nature, a reduction in the levels of enzymes that counteract pro-oxidant complexes as well as a decline in scavengers of free radicals. In several previous studies berberine is beneficial in reducing oxidative stress and its associated disorders. Berberine specifically suppress the generation of reactive species and also increase the level of enzymes responsible for compounds of pro-oxidation. In turn berberine also upsurge the scavengers of free radicals and oxidation reactions as well.[20]

Nephroprotective effect

Chronic kidney damage that develops over time in patients with hypertension (HT) and diabetes mellitus (DM) is widely recognized. Oxygen Reactive Species elevation, increased inflammation of renal cells & apoptosis process is specific reasons of kidney damage. All these factors are suppressed by the treatment of berberine as showed by varied researchers. [21]

Anti-arthritic activity

Arthritis is the most prevalent disease worldwide, with more than 300 million reported cases. Arthritis arises from damage to the cartilage that cushions and protects the joints. Arthritis causes synovial cell hyperplasia along with an inflammatory response. In arthritis due to activation of immune system there is an increased inflammation due to upsurge in inflammatory mediators such as tumour necrosis factors and interleukins. Berberine showed suppressive effects on the production of mediators of inflammatory reactions thus producing anti-arthritic effect.[19, 22]

Anti-bacterial activity

Berberine, an active compound in the traditional Chinese medicine, plays a crucial role in safeguarding mammals from bacterial infections. Infections have historically been a major cause of disease, with bacterial infections in particular posing a significant threat to human health, often leading to considerable illness and death. Bacterial infections can trigger inflammation in various organs, such as glomerulonephritis resulting from *streptococcal* as well as *staphylococcal* infections, many of which may progress to chronic kidney disease or end-stage renal disease. *Staphylococcus aureus* is commonly linked to influenzas well as bacterial co-infections in individuals, which can worsen the condition and lead to severe complications or death. Pneumonia caused by K. pneumoniae, urinary tract infections from gram-negative bacteria, and acute infections associated with various bacteria have the potential to develop into multiple myeloma. Many studies showed that berberine is having potential effects such as disruption of cell membrane, DNA as well as RNA synthesis inhibition, and also the bacterial metabolic pathways interruptions.[23]

Anti-cancer activity

Cancer is a complex disease characterized by the uncontrolled growth of abnormal cells, which have the ability to spread throughout the body. The mortality rate from this devastating disease is increasing quickly, and by the year 2030, it is estimated that there will be more than 25 million new cancer cases and 16.5 million deaths annually associated with cancer. Cancer can develop due to a variety of factors, including internal ones such as predisposition of genes, hormone imbalances, increasing age, mutations of cells, and ill conditions of immune system. Exogenous or acquired factors that contribute to cancer include nutritional imbalance, environmental changes, choices in lifestyle, irregular diet, use of tobacco, obesity, exposure to sun, environmental chemicals & radiation, as well as groupings of these elements. In previous studies berberine showed suppression of ROS generation and upsurge in apoptotic processes as well as regulation of cell cycle, which makes them a potential anticancer agent. Berberine also showed inhibition of various steps important in carcinogenesis there by inhibit progression as well as development of cancer.[24]

Anti-depressions activity

Depression is a prevalent mental health disorder marked by a long-lasting and powerful low mood, along with cognitive & behavioural as well as social impairments. It is a debilitating condition with a high prevalence and disability rate, affecting 20% of people globally over their lifetime, and placing a significant emotional and economic strain on both society & families. The primary symptoms in patients include emotional instability, loss of interest or pleasure (anhedonia), difficulty concentrating, and a predisposition toward suicidal behaviour. Existing treatments are not sufficiently effective in reducing the morbidity and mortality linked to depression and have limited success in managing the condition. There is growing evidence suggesting that inflammation plays a role in the development of depression, including increased levels of various markers of pro-inflammatory & physical comorbidities in individuals with

depression. Chronic inflammatory signalling may negatively impact conditions that are linked to depression and other mental health disorders. Inflammasomes, like the NOD-like receptor family pyrin domain containing 3 (NLRP3), are key complexes intricate in the response of inflammation. When activated, apoptosis-associated speckle-like protein (ASC) and NLRP3 combine to form multimeric proteins called the NLRP3 inflammasome. Inflammatory cytokines activated by the NLRP3 inflammasome complex are believed to play a central role in the development or worsening of psychiatric disorders. Recent studies indicate that berberine specifically interferes with the NEK7-NLRP3 interactions and directly inhibits oligomerization of ASC as well as activation of NLRP3 inflammasome. This steps proved the beneficial effect of berberine on depression. [25]

Anti-obesity activity

Obesity is a component of metabolic syndrome, along with hypertension, resistance of insulin, and dyslipidaemia. Its rising prevalence heightens the risk of cardiovascular diseases and various cancers, resulting in significant public health expenses. Obesity is a long-term condition defined by excessive fat accumulation that can negatively impact health. The rate of obesity is growing speedily. The rising prevalence of overweight and obese individuals has become a significant global concern, contributing to an estimated more than 3.3 million deaths. Obesity arises from multiple factors, including genes, hormonal imbalances, and environmental influences. Obesity is linked to a heightened risk of various comorbidities, including diabetes mellitus, cardiovascular & respiratory disorders, few types of cancers, as well as psychological and social disorders. Previous studies on berberine reported that berberine supresses the inflammatory reactions, inhibits the generation of adipocytes, promotes expenditure of body's energy, modulation of microbiota of gut and also augment the resistance of insulin. [26]

Conclusion:

Herbal supplements, vitamins, and natural medicines are consumed and absorbed to prevent various illnesses and ailments. India has a long-standing tradition of herbal medicine, as demonstrated by Ayurveda, which has thrived for over 2000 years, suggesting a foundation in scientific principles. Over 80% of the global population depends exclusively on medicinal plants to meet their primary healthcare needs. Additionally, these natural substances are easily accessible, affordable, and generally free from the adverse side effects commonly linked to synthetic drugs. Some of these herbs have been shown to offer symptomatic relief and aid in preventing secondary complications of diseases, while others are reported to support the regeneration of abnormal cells and combat disease-causing pathogens. Throughout history, plants have been an important source of affordable natural compounds, especially secondary metabolites. Many of these pharmaceuticals are synthetically produced, while others are derived directly from plants. Alkaloids are a chemically varied and biologically active class of natural compounds with considerable therapeutic potential. Their intricate structures, often featuring nitrogen-containing rings, support a wide range of pharmacological activities, making them indispensable in medicine for centuries. Their involvement in plant defence mechanisms and

interactions with biological systems has shed light on their evolutionary importance. Based on the review, it can be concluded that berberine the active component of *Berberis aristata* is a valuable phytochemical with a rich history and considerable potential for treating various health conditions, supported by both traditional indigenous knowledge and scientific research. Phytochemicals encompass a broad spectrum of therapeutic applications and exhibit remarkable chemical diversity. As a result, they serve as valuable leads for the development of new drug candidates in the fields of drug design and discovery. Berberine is a plant-derived compound from the isoquinoline alkaloid group, known for its potent biological and pharmacological properties. The current study showed that berberine is having pharmacological effects in various ailments such as cancer, bacterial infection, oxidative stress and inflammatory reactions associated diseases, as well as obesity and autoimmune disorders. These qualities make it an ideal therapeutic component as an alternative to traditional medicine. Additional research and clinical studies are necessary to thoroughly investigate and confirm the therapeutic potential as well as pharmacokinetic parameters of berberine.

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HERBAL NANOCARRIERS: ADVANCES IN PHYTOPHARMACEUTICAL DRUG DELIVERY SYSTEMS

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Abstract:

Herbal medicines have long been an integral part of traditional therapeutic practices worldwide. Despite their widespread use, phytoconstituents often suffer from limitations such as poor aqueous solubility, low bioavailability, instability and rapid metabolism which hinder their clinical effectiveness. Recent advances in nanotechnology have paved the way for overcoming these challenges through the development of herbal nanocarriers as an innovative delivery system that encapsulate herbal extracts and bioactive compounds within nanoscale carriers. This chapter explores the progress made in the field of herbal nanocarriers, highlighting various nanocarrier systems including liposomes, phytosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, nanoemulsions and dendrimers. This chapter elucidates the mechanisms by which nanocarriers enhance the pharmacokinetic and pharmacodynamic properties of phytochemicals, with additional focus on targeted delivery, controlled release and increased permeation. Also addresses challenges in formulating herbal nanocarriers, such as stability concerns, scalability, regulatory issues and quality control. Case studies of successful herbal nanocarrier-based formulations are presented to illustrate practical applications in areas like anti-inflammatory therapy, anticancer treatment, and neuroprotection. Emerging trends including green synthesis of nanoparticles and hybrid nanocarriers are also explored, emphasizing their potential in the next generation of phytopharmaceuticals. This comprehensive chapter offers valuable insights to harness the full potential of herbal medicines through advanced drug delivery systems.

Keywords: Herbal Nanocarriers, Liposomes, Phytosomes, Solid Lipid Nanoparticles, Targeted Delivery

Introduction:

Herbal medicines have served as the cornerstone of healthcare in many cultures for thousands of years, forming the foundation of traditional medical systems such as Ayurveda, Traditional Chinese Medicine (TCM), Unani, Siddha, and various indigenous healing practices worldwide. These systems harness a vast diversity of plant species, utilizing roots, leaves, bark, seeds, and flowers for therapeutic purposes. The pharmacological activity of these herbal remedies is attributed to a wide range of bioactive compounds, collectively known as phytochemicals, which include alkaloids, flavonoids, saponins, tannins, glycosides, terpenoids,

and polyphenols. These phytochemicals have been scientifically validated to exert a broad spectrum of therapeutic effects, such as anti-inflammatory, antioxidant, antimicrobial, anticancer, antidiabetic, hepatoprotective, cardioprotective, and neuroprotective activities. For example, curcumin (turmeric) is renowned for its potent anti-inflammatory and antitumor activity; resveratrol (grapes) is identified for its antioxidant and cardioprotective effects; and ginsenosides (ginseng) are noted for their neuroprotective and adaptogenic activities. [1] The global resurgence of interest in herbal medicines is driven by several factors: increased public demand for sustainable and integrative approaches to health, increased scientific data supporting the effectiveness of phytopharmaceuticals, and increasing concerns about the side effects and resistance linked to synthetic medicines. [2]

Despite the vast therapeutic promise of herbal medicines, their clinical application is affected by significant biopharmaceutical and pharmacokinetic challenges. A major issue is the poor aqueous solubility of many phytochemicals, which limits their dissolution in biological fluids and, consequently, their absorption in the gastrointestinal tract. Compounds such as curcumin, quercetin, and silymarin exhibit very low water solubility, resulting in subtherapeutic plasma concentrations even after high oral doses. Another main limitation is restricted membrane permeability, which impedes the efficient transport of phytochemicals across biological barriers such as blood-brain barrier and intestinal mucosa. [3] Furthermore, many phytoconstituents are chemically unstable and prone to degradation in physiological conditions factors such as pH variations, enzymatic hydrolysis, oxidation, and light exposure can compromise their stability and therapeutic efficacy. In addition, rapid metabolism by intestinal and hepatic enzymes (first-pass metabolism) significantly reduces the systemic availability of many herbal compounds. For instance, curcumin undergoes extensive metabolism to inactive forms, limiting its bioavailability to less than 1% following oral administration. These limitations often necessitate the use of high doses to achieve therapeutic effects, which can paradoxically increase the risk of adverse effects and toxicity. Moreover, the complexity and variability of herbal extracts which can contain dozens to hundreds of phytochemicals pose challenges for standardization, quality control, and reproducibility of therapeutic outcomes. The variability in plant species, cultivation conditions, harvesting times, and extraction methods further complicates the development of consistent and reliable herbal products. [4]

Need for nanocarrier-based delivery systems

Challenges in herbal drug delivery

The delivery of herbal compounds in their natural or raw form presents several pharmacokinetic and pharmacodynamic challenges that limit their therapeutic efficacy, primarily due to the inherent physicochemical properties of the phytochemicals and their complex interactions within the body. One of the main obstacles is poor solubility, as many bioactive compounds, such as curcumin, resveratrol, and quercetin, are lipophilic and do not dissolve well in water, resulting in limited dissolution in the gastrointestinal (GI) tract and hindering absorption. This leads to low systemic bioavailability, and only the small dose reaches the

bloodstream in its active form, requiring higher doses to achieve therapeutic effects, which increases the risk of toxicity and side effects. [5] Herbal compounds undergo rapid chemical degradation in the GI tract, due to the acidic environment of the stomach, and are prone to enzymatic degradation and reduces their therapeutic potential. For example, curcumin is highly susceptible to hydrolysis and oxidation, leading to reduced active compound levels. Many herbal compounds are subject to first-pass metabolism in the liver, further diminishing bioavailability and causing inconsistent drug levels and variable therapeutic responses. [6] Even when herbal compounds survive degradation, their absorption through the intestinal mucosa is inefficient due to barriers such as tight junctions between epithelial cells and the presence of efflux transporters like P-glycoprotein, which actively pump out foreign compounds. Additionally, many herbal extracts contain multiple active constituents that can interact in complex ways, with some enhancing or inhibiting the absorption and activity of others, complicating the prediction of their pharmacokinetic behavior and leading to inconsistent therapeutic outcomes. [7]

Advantages of herbal drug delivery

Incorporating herbal compounds into nanocarrier systems significantly improves therapeutic outcomes, safety and patient compliance. One of the key advantages is enhanced bioavailability, as nanocarriers increase the solubility and absorption of poorly water-soluble phytochemicals like curcumin and resveratrol by encapsulating them within lipidic or polymeric matrices. These carriers also protect sensitive compounds from degradation caused by pH, enzymes, oxidation and light, preserving their therapeutic potential. Nanotechnology enables controlled and sustained release of herbal drugs by allowing modulation of carrier properties to achieve targeted and prolonged therapeutic effects, which is especially beneficial in chronic conditions. [8,9] Targeted delivery is another critical advantage, with surface-functionalized nanocarriers capable of delivering drugs specifically to diseased cells or tissues, such as tumors, thereby minimizing side effects and enhancing efficacy. Nanoparticles improve cellular uptake and allow deeper tissue penetration, even across complex barriers like the blood-brain barrier, facilitating treatments for neurological conditions. The ability to co-deliver multiple phytochemicals or herbal-synthetic combinations within a single carrier promotes synergistic effects and hybrid therapies. The improved delivery efficiency enables dose reduction, lowering the risk of toxicity and enhancing patient safety. With multiple administration routes including oral, transdermal, and intravenous, nanocarriers increase flexibility and patient adherence to treatment. [10]

Types of herbal nanocarriers

Nanocarriers are nanoscale systems engineered to transport bioactive compounds efficiently to their site of action. In herbal drug delivery, these systems are employed to encapsulate, protect, and deliver phytochemicals in a controlled and targeted manner. Various types of nanocarriers have been developed to address the specific physicochemical and therapeutic needs of different herbal compounds Figure 1. The most prominent types include:

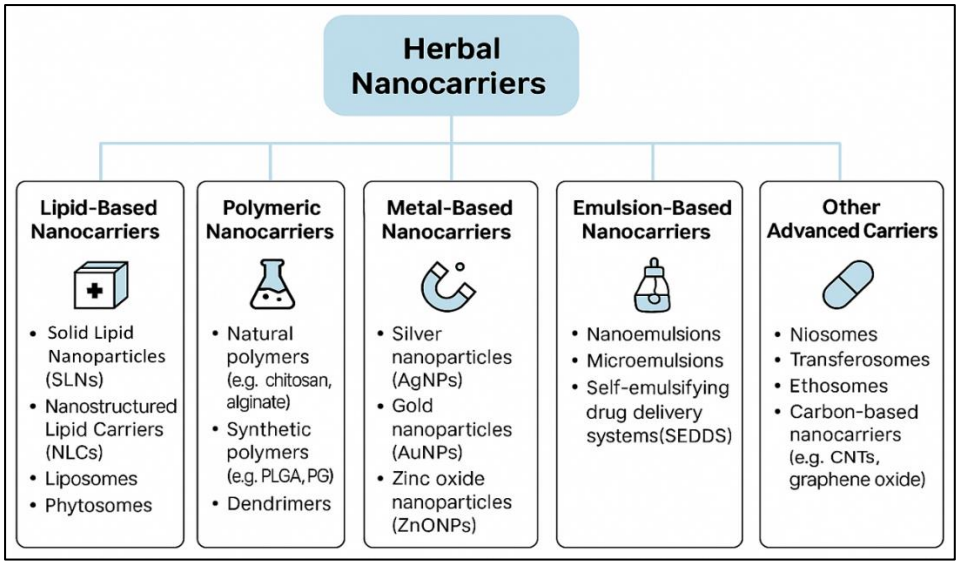

Figure 1: Different types of herbal nanocarriers

Liposomes

Liposomes are spherical vesicles with an aqueous core surrounded by one or more bilayers of phospholipids. Due to their structural similarity to biological membranes, liposomes are biocompatible and can incorporate both hydrophilic compounds (in the aqueous core) and lipophilic compounds (within the lipid bilayer). This dual encapsulation capacity makes them ideal for a broad spectrum of herbal extracts. Liposomes improve drug solubility, protect phytochemicals from enzymatic degradation, and enhance their bioavailability by facilitating fusion with cell membranes. For example, liposomal formulations of curcumin, quercetin, and glycyrrhizin have demonstrated improved systemic absorption and enhanced anti-inflammatory or anticancer effects. Surface modification with targeting ligands (e.g., folate or antibodies) can further enhance tissue-specific delivery. [11]

Phytosomes

Phytosomes are molecular complexes formed by the interaction of phytochemicals, especially polyphenols and flavonoids, with phospholipids, most commonly phosphatidylcholine. Unlike liposomes, where the drug is physically entrapped, phytosomes involve the formation of hydrogen bonds between the active ingredient and the phospholipid, resulting in improved bioavailability and membrane permeability. This is particularly useful for poorly absorbed herbal compounds. For instance, silymarin–phospholipid complexes have shown significantly better hepatoprotective activity compared to silymarin alone due to enhanced absorption. Similarly, curcumin phytosomes have exhibited greater therapeutic efficacy in inflammation and metabolic disorders. [12]

Solid lipid nanoparticles (SLNs)

Solid lipids (such as stearic acid and glyceryl monostearate) that are stabilised by surfactants and present as solid at room temperature and body temperature make up solid lipid nanoparticles, which are submicron colloidal carriers. SLNs combine the advantages of liposomes and polymeric nanoparticles, such as controlled release and high biocompatibility, while avoiding disadvantages like drug leakage and stability issues. SLNs can protect labile

herbal bioactives from chemical degradation and improve their pharmacokinetic profiles. For example, berberine-loaded SLNs have shown better antihyperglycemic effects, and thymoquinone-SLNs have demonstrated prolonged anti-inflammatory activity in preclinical models. [13]

Nanostructured lipid carriers (NLCs)

NLCs are second-generation lipid nanoparticles consisting of both solid and liquid lipids in their matrix, leading to a more disordered crystalline structure. This imperfection in the lipid matrix allows the enhanced drug loading and reduces drug expulsion during storage, a common limitation in SLNs. NLCs provide sustained and controlled release of herbal drugs and are highly stable during long-term storage. They are particularly useful for lipophilic phytoconstituents such as boswellic acids, artemisinin, and andrographolide. These systems have shown promise in dermal, oral, and parenteral delivery routes, enhancing bioavailability and therapeutic targeting. [14]

Nanoemulsions

Nanoemulsions are fine oil-in-water or water-in-oil emulsions with droplet sizes typically ranging from 20 to 200 nm. They consist of oils, surfactants, and aqueous phases, and are characterized by high kinetic stability, transparency, and low viscosity. Nanoemulsions enhance the solubility and absorption of lipophilic herbal constituents and can be administered via various routes including oral, topical, and parenteral. For example, nanoemulsions containing turmeric oil, eucalyptus oil, or black seed oil have been evaluated for their potent antimicrobial, antifungal, and wound healing activities. [15] Their ease of preparation and scalability make them particularly attractive for industrial applications.

Dendrimers

Dendrimers are monodisperse, highly branched macromolecules that resemble trees and are made up of many surfaces functional groups, a central core, and repeating branching units called generations. These structures offer precise control over size, surface charge, and functionality, making them ideal for drug encapsulation, conjugation, and targeted delivery. Dendrimers can encapsulate herbal drugs within their internal cavities or bind them to surface groups, providing high payload and controlled release. While still in early stages of application in phytomedicine, dendrimers have shown promise for delivering catechins, alkaloids, and other bioactive herbal compounds in cancer and inflammation models. [16]

Metallic and inorganic nanoparticles (e.g., Gold, Silver, Silica)

Although primarily investigated for diagnostic and imaging purposes, metallic nanoparticles such as gold and silver are being explored as delivery systems for herbal compounds due to their unique optical and physicochemical properties. It can be synthesized using green methods involving herbal extracts themselves, thus serving dual functions as both carrier and active ingredient. Silica nanoparticles, particularly mesoporous silica, are being used for loading phytoconstituents like gallic acid and curcumin, offering high loading capacity and controlled release. [17,18]

Nanofibers and Nanogels

Nanofibers are ultrafine fibers fabricated using electrospinning techniques and are used for transdermal or wound healing applications. Herbal extracts such as aloe vera, neem, and curcumin have been successfully incorporated into nanofiber mats for enhanced healing. Nanogels, on the other hand, are hydrogel-based nanosystems that can swell in aqueous environments and provide site-specific and stimuli-responsive drug release. Herbal nanogels are being developed for topical applications in dermatology and for mucosal drug delivery. [19]

Mechanisms of improved drug delivery via nanocarriers

Nanocarrier systems enhance the therapeutic potential of herbal medicines by overcoming several biological, chemical, and physical barriers that limit the effectiveness of conventional phytopharmaceutical formulations. The nanoscale size, tailored surface properties, and intelligent design of these carriers allow for improved delivery, targeting, and performance of herbal compounds. The primary mechanisms through which nanocarriers improve herbal drug delivery include:

Enhanced Permeation and Retention (EPR) Effect

This is mainly relevant in tumors and inflamed tissues, which exhibit leaky vasculature and impaired lymphatic drainage. Nanoparticles in the size range of 10-200 nm can exploit these abnormalities to preferentially localize at disease sites. Herbal-loaded nanocarriers such as curcumin-loaded liposomes or resveratrol-loaded solid lipid nanoparticles have demonstrated improved tumor accumulation via the EPR mechanism, leading to higher local drug concentrations and enhanced therapeutic efficacy. [20]

Improved solubility and dissolution

Many herbal drugs, including flavonoids, polyphenols, and terpenoids, exhibit low aqueous solubility, which severely limits their absorption and bioavailability. Nanocarriers improve solubility by encapsulating these hydrophobic phytoconstituents in lipid or polymer matrices, which disperse well in aqueous environments. This leads to a higher apparent solubility and faster dissolution rate. For example, poorly soluble drugs like quercetin and silymarin, when loaded into nanoemulsions or polymeric nanoparticles, show significantly improved solubility and faster onset of action. [21]

Protection from enzymatic and chemical degradation

Phytoconstituents are often unstable in the harsh gastrointestinal environment or susceptible to enzymatic breakdown and oxidation. Nanocarriers act as protective shields, isolating these compounds from degradative conditions. For instance, nanoencapsulation of epigallocatechin gallate (EGCG) or thymoquinone within SLN or liposomes has shown significant resistance to degradation, thereby enhancing stability, shelf life, and systemic availability. [22]

Increased mucosal adhesion and residence time

Certain nanocarriers, especially those made from mucoadhesive polymers like chitosan or alginate, can adhere to mucosal surfaces (e.g., in the gastrointestinal tract or nasal cavity), thereby prolonging the residence time of the drug. This improves absorption and bioavailability.

For example, chitosan nanoparticles loaded with gingerol or berberine have demonstrated prolonged intestinal retention and enhanced uptake due to strong interaction with mucosal surfaces. [23]

Receptor-mediated and active targeting

Nanocarriers can be surface-functionalized with ligands such as antibodies, peptides, or small molecules that selectively bind to receptors overexpressed on target cells or tissues. This receptor-mediated endocytosis enables active targeting of diseases like cancer, inflammation, or neurodegenerative disorders. For instance, folic acid-conjugated nanoparticles can target folate receptors on cancer cells, enabling the targeted delivery of herbal drugs like curcumin or ginsenoside. Similarly, transferrin- or lactoferrin-functionalized nanoparticles are being investigated for crossing the blood-brain barrier in neurodegenerative therapy. [24]

Bypassing efflux pumps and metabolic barriers

Efflux transporters like P-glycoprotein (P-gp) in the intestinal epithelium often pump out foreign substances, including herbal compounds, reducing their bioavailability. Nanocarriers can mask the phytochemicals from these transporters or inhibit their action, thereby enhancing absorption. Additionally, encapsulation may reduce the first-pass metabolism in the liver by avoiding rapid recognition and degradation by metabolic enzymes. This has been observed in formulations of piperine, curcumin, and other compounds that are otherwise rapidly metabolized. [25]

Co-delivery and synergistic action

Nanocarriers can be designed to encapsulate more than one active component, allowing for the co-delivery of synergistic phytochemicals or herbal-synthetic drug combinations. This ensures synchronized release and action at the target site, maximizing therapeutic effects while minimizing the risk of drug-drug interactions. Co-delivery systems such as curcumin-resveratrol nanoformulations or quercetin-paclitaxel nanoparticles have shown enhanced anticancer synergy. [26]

Formulation strategies and characterization techniques

Formulation strategies

Selection of nanocarrier type and materials

The initial step in developing a nanocarrier-based herbal formulation is selecting the appropriate carrier type and constituent materials. This choice is dictated by several factors, including the physicochemical properties of the herbal active (solubility, molecular weight, stability), the intended route of administration, and the therapeutic objective. Lipid-based nanocarriers such as SLNs, NLCs and nanoemulsions are mainly suitable for hydrophobic and poorly water-soluble herbal compounds like curcumin, resveratrol, and boswellic acids, as they enhance solubility and absorption. In contrast, polymeric nanoparticles, specifically those made from biodegradable polymers like chitosan, alginate, PLGA and gelatin, are more suitable for encapsulating hydrophilic and thermolabile compounds due to their strong protective matrices and customizable degradation profiles. [27] Natural polymers are increasingly favored due to their biocompatibility, biodegradability and regulatory acceptance. Chitosan, for instance, offers

mucoadhesive properties and can transiently open tight junctions in the intestinal epithelium, enhancing paracellular transport of herbal actives.

Encapsulation techniques

The encapsulation technique directly impacts nanoparticle morphology, drug loading efficiency, release kinetics, and stability. The method is selected based on the carrier type, drug solubility, and desired release profile:

- High-pressure homogenization and microfluidization are commonly used for preparing SLNs and NLCs, allowing uniform particle sizes and scalable production.
- Solvent evaporation, nanoprecipitation and emulsification-solvent diffusion techniques are employed for polymeric nanoparticles, enabling high drug loading and tunable release.
- Thin-film hydration and reverse-phase evaporation are classic methods for liposome preparation, offering control over bilayer composition and vesicle size.
- Spontaneous emulsification and ultrasonication are used for nanoemulsions, resulting in fine droplets and kinetically stable systems.

An important performance metric is encapsulation efficiency (EE%), which measures the proportion of drug successfully incorporated into the carrier system. EE is influenced by factors such as drug-to-carrier ratio, solubility of the drug in the lipid/polymer phase, and the polarity of solvents used during preparation. Maximizing EE is crucial for maintaining therapeutic efficacy and minimizing waste. [28]

Surface functionalization

To enhance targeting, circulation time, or site-specific retention, nanocarriers are often modified on their surface. Functionalization not only enhances the targeting ability of nanocarriers but can also improve their colloidal stability and biocompatibility. [28] This process, known as surface functionalization, introduces specific chemical groups or ligands that impart desired bio-interactive properties:

- The addition of polyethylene glycol chains, or PEGylation, lengthens the duration that substances circulate throughout the body by decreasing the ability of reticuloendothelial systems (RES) to recognise and eliminate them.
- Active targeting of cancer cells, inflammatory tissues, or certain receptors overexpressed in pathological situations is made possible by ligand conjugation with targeting moieties such as folic acid, transferrin, hyaluronic acid, or peptides.
- Mucoadhesive polymers, such as chitosan, can be used to improve gastrointestinal residence time, thereby enhancing oral bioavailability of herbal formulations.

Stability enhancement

Many herbal compounds are inherently unstable and prone to degradation due to oxidation, hydrolysis, heat, light, or pH fluctuations. Formulation strategies to improve the physicochemical stability of herbal nanocarriers include:

- Incorporating natural antioxidants like tocopherol, ascorbic acid, or rosemary extract to protect against oxidative degradation.

- Lyophilization (freeze-drying) of nanoparticle dispersions into powders for extended shelf life and improved storage stability. Cryoprotectants such as mannitol or trehalose are typically added during freeze-drying to preserve nanoparticle structure.
- Use of amber-colored or opaque packaging and pH-stabilized excipients to minimize photolysis and chemical degradation during storage.[29]

Characterization techniques

Particle size and size distribution

Size influences nanoparticle uptake, circulation time, biodistribution, and cellular interaction. Ideally, particle sizes <200 nm are optimal for intravenous or tumor-targeted delivery, while <500 nm is acceptable for dermal or oral formulations.

- Dynamic light scattering (DLS) is a widely used technique for measuring average particle size, polydispersity index (PDI) and zeta potential. A PDI value <0.3 indicates a uniform particle distribution. [30]
- Nanoparticle tracking analysis (NTA): Provides high-resolution real-time tracking of individual particles in suspension, offering insights into size distribution and concentration.

Surface charge

Zeta potential reflects the electrostatic potential at the nanoparticle surface and is indicative of colloidal stability. A zeta potential > ±30 mV is generally considered stable, as it reduces the likelihood of particle aggregation. Surface charge also affects interactions with biological membranes and proteins. [31]

Morphology and structural analysis

These techniques are crucial for confirming the expected morphology of liposomes, nanospheres, or dendrimers.

- Transmission electron microscopy (TEM) and Scanning electron microscopy (SEM) are used to perform the structural analysis which provide high-resolution images of nanoparticles, allowing evaluation of shape, surface texture, and aggregation.
- Atomic force microscopy (AFM) offers 3D surface topography at the nanoscale and can reveal fine surface characteristics and structural uniformity. [32]

Encapsulation efficiency and drug loading

Drug loading efficiency is equally critical, as it determines the therapeutic dose per unit of nanocarrier. Quantification of herbal drug encapsulation is typically performed using:

- UV-vis spectrophotometry is a simple and cost-effective, suitable for compounds with strong chromophores used to evaluate encapsulation efficiency and drug loading.
- High-performance liquid chromatography (HPLC) and Liquid chromatography-mass spectrometry (LC-MS/MS) that provide precise quantification, especially for complex plant-derived mixtures. [33]

Stability studies

Stability studies under ICH (International council for harmonisation) conditions (e.g., 25°C/60% RH, 40°C/75% RH) assess changes in physical appearance, particle size, zeta potential, encapsulation efficiency, and drug content over time. These studies determine the

product's shelf life and guide optimal packaging and storage. [34] Clinical applications of herbal nanocarriers are shown in Table 1.

Table 1: Clinical and preclinical applications of herbal nanocarriers. [35,36]

Therapeutic action	Herbal drug/extract	Nanocarrier type	Research outcome
Anti-inflammatory	Curcumin	Liposomes, SLNs, NLCs	Improved bioavailability, enhanced anti-inflammatory effect, reduced oxidative stress
	Boswellic acid	NLCs, Nanoemulsions	Sustained release, effective inflammation control in arthritis models
	Gingerol	Chitosan nanoparticles	Enhanced GI absorption, reduced gastric inflammation
Anticancer	Resveratrol	SLNs, PLGA nanoparticles	Increased cytotoxicity to cancer cells, tumor targeting via EPR effect
	Quercetin	Liposomes, Polymeric NPs	Synergistic anticancer activity, improved cellular uptake
	EGCG (green tea polyphenol)	Polymeric nanoparticles	Targeted delivery to tumors, apoptosis induction in cancer cells
Neuroprotective	Ginsenosides	Polymeric micelles, NLCs	BBB penetration, neuroprotective effect in Alzheimer's and Parkinson's models
	Bacopa monnieri extract	Nanoemulsion	Enhanced cognitive function, better bioavailability in CNS delivery
Antidiabetic	Berberine	SLNs, PLGA nanoparticles	Improved hypoglycemic effect, prolonged circulation time
Hepatoprotective	Silymarin	Phytosomes, Liposomes	Enhanced liver targeting, increased protection against hepatotoxins
Cardioprotective	Terminalia arjuna extract	Nanoemulsion, SLNs	Improved antioxidant activity, reduced myocardial damage
Antimicrobial / Wound Healing	Neem, Turmeric oil	Nanoemulsion, Nanofibers	Potent antimicrobial activity, faster wound healing, improved skin permeation
Skin Disorders	Aloe vera, Tea tree oil	Nanogels, Liposomes	Anti-inflammatory, antimicrobial effect, enhanced dermal absorption

Conclusion:

Herbal compounds, though therapeutically potent are often hindered by poor solubility, low bioavailability, chemical instability and limited tissue penetration. Nanocarrier systems such as liposomes, phytosomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions and dendrimers have emerged as powerful tools to address these challenges. These carriers not only protect herbal actives from degradation but also enhance their absorption, target specific tissues, and provide controlled or sustained release profiles, thereby maximizing therapeutic efficacy while minimizing side effects. The strategic formulation and characterization of herbal nanocarriers play a pivotal role in ensuring their stability, safety, and performance. Advances in encapsulation techniques, surface modification, and stability optimization have further contributed to the scalability and clinical readiness of these systems. Numerous preclinical and some clinical studies have demonstrated promising outcomes across various therapeutic areas, including oncology, neuroprotection, inflammation, and metabolic disorders. Despite the encouraging progress, challenges remain particularly in terms of large-scale manufacturing, regulatory standardization, and comprehensive toxicity profiling. Nonetheless, the future of herbal nanomedicine is promising, especially with emerging trends such as green synthesis, hybrid nanocarriers, and personalized nanotherapy. As herbal nanocarriers continue to evolve, they hold immense potential to bridge traditional medicine and modern pharmaceutical science, offering safer, more effective, and patient-friendly therapeutic options for a wide range of diseases.

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THERAPEUTIC ROLE OF MEDICINAL SEEDS IN PCOD: PHYTOESTROGENS, HORMONAL BALANCE, AND METABOLIC MODULATION

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Abstract:

Polycystic Ovarian Disease (PCOD), also known as Polycystic Ovary Syndrome (PCOS), is a prevalent endocrine disorder among women of reproductive age, categorized by hormonal imbalance, uneven menstrual cycles, and metabolic instabilities. Recent research highlights the therapeutic role of plant-based interventions in its management. Seeds such as *flaxseed*, *fenugreek*, *nigella sativa* (black seed), *chia*, and *pumpkin* are loaded with phytoestrogens, essential fatty acids, lignans, and anti-inflammatory amalgams that modulate insulin resistance, lower androgens, and regulate menstrual function. This chapter explores the pharmacological potential of these seeds and their phytoconstituents in mitigating PCOD symptoms, focusing on their hormonal, metabolic, and anti-inflammatory effects. Emphasis is placed on mechanistic insights and comparative efficacy with standard pharmacotherapy, offering a basis for integrative and nutraceutical strategies in PCOD care.

Keywords: Polycystic Ovarian Disease (PCOD)**,** Herbal seeds**,** Phytochemicals**,** Phytoestrogens**,** Fenugreek (*Trigonella foenum-graecum)*

Introduction:

PCOD is a prevalent endocrine disorder occuring approximately 8–13% of women of reproductive age globally, with even higher pervasiveness reported in South Asian populations. In countries like India, studies suggest that 1 in 5 women may suffer from PCOD, highlighting its growing public health concern.[1] Characterized by hormonal imbalances, chronic anovulation, polycystic ovaries, and hyperandrogenism, PCOD manifests through a range of symptoms including irregular menstrual cycles, infertility, hirsutism, acne, obesity, and insulin resistance. Beyond reproductive issues, it poses long-term risks such as type 2 diabetes, cardiovascular disease, and endometrial cancer, significantly affecting the quality of life and imposing both emotional and economic burdens on patients and healthcare systems. Despite advances in modern medicine, the current therapeutic strategies for PCOD remain largely symptomatic. Standard treatments include hormonal contraceptives to control menstrual cycles, anti-androgens to decrease extreme hair growth, and insulin-sensitizing agents like metformin to manage metabolic dysfunction. While these interventions can be effective, they often come with undesirable adverse effects such as nausea, mood swings, increase in weight, and long-term

hormonal disturbances. Moreover, conventional therapies do not resolve the main cause of PCOD and are generally not curative. Many women express dissatisfaction with the continuing use of synthetic drugs and seek safer, more holistic alternatives that support overall health, hormonal balance, and fertility.

In this context, herbal remedies have gained increasing attention as a promising alternative or complementary approach in PCOD management.[2] Among these, seeds like flaxseed, fenugreek, chia, pumpkin, and *Nigella sativa* have demonstrated significant medicinal potential due to their rich content of phytoestrogens, omega-3 fatty acids, lignans, flavonoids, and other bioactive compounds. These phytoconstituents exhibit hormone-regulating, insulin-sensitizing, anti-inflammatory, and antioxidant potential, which can help address the multifactorial nature of PCOD. Furthermore, traditional practices like seed cycling timed consumption of specific seeds during the menstrual cycle are increasingly recognized for their role in naturally balancing estrogen and progesterone levels. As interest in nutraceuticals and plant-based interventions grows, there is a pressing need for scientific evaluation of seed-based therapies in PCOD, paving the way for integrative, evidence-based alternatives to conventional treatments.

Role of seeds in hormonal regulation

Hormonal imbalance is central to the pathophysiology of PCOD, primarily involving elevated androgens, disrupted estrogen-progesterone ratios, and impaired insulin signaling. In recent years, seeds have emerged as potent natural agents capable of influencing hormonal pathways due to their unique phytochemical profiles. Seeds such as flaxseed, fenugreek, chia, pumpkin, and *Nigella sativa* (black seed) are particularly loaded with phytoestrogens plant-derived compounds that resembles the action of estrogen in the body. These phytoestrogens, especially lignans found in flaxseed, modulate estrogen metabolism and bind to estrogen receptors, thus helping to restore hormonal balance.[3] Fenugreek seeds contain saponins and diosgenin, known to support ovulation and reduce hyperandrogenism by regulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. Chia seeds, high in omega-3 fatty acids, have anti-inflammatory potential that may alleviate symptoms of PCOD such as insulin resistance and menstrual irregularity. Moreover, the concept of “seed cycling” has gained popularity as a natural method to balance female reproductive hormones throughout the menstrual cycle. This practice involves consuming flaxseed and pumpkin seeds during the follicular phase (day 1 to 14) to promote estrogen production, and sunflower and sesame seeds during the luteal phase (day 15 to 28) to encourage progesterone levels.[4] The cyclic pattern mimics the natural hormonal fluctuations and can be particularly beneficial for women with irregular cycles or hormonal imbalances. Beyond hormonal effects, seeds also provide dietary fiber, essential minerals like zinc and magnesium, and antioxidants, all of which contribute to improved ovarian function and metabolic stability. Thus, the integration of seeds in daily nutrition presents a safe, accessible, and potentially effective strategy to regulate hormonal disturbances in PCOD.

Pharmacological profiles of individual seeds in PCOD management

A. Flaxseed: lignans and estrogen modulation

Flaxseeds (*Linum usitatissimum*) are one of the richest natural sources of lignans specifically *secoisolariciresinol diglucoside (SDG)* which are categorized as phytoestrogens.[5] These plant-derived complexes structurally look like estrogen and can bind to estrogen receptors in the body, allowing them to either exert weak estrogenic effects or block excess estrogen depending on the hormonal environment. In women with PCOD, where estrogen dominance and anovulation are common, flaxseed lignans help in restoring hormonal equilibrium by enhancing estrogen metabolism and augmenting the levels of sex hormone-binding globulin (SHBG), which binds free testosterone and reduces its bioavailability. Moreover, flaxseeds contribute to menstrual regularity, reduce symptoms of hyperandrogenism (like acne and hirsutism), and provide alpha-linolenic acid (ALA)—an omega-3 fatty acid that decreases systemic inflammation and promotes ovarian function. Their high dietary fiber also contributes to improved insulin sensitivity and better gut health, both crucial for PCOD management.

B. Fenugreek: insulin sensitization and ovulation

Fenugreek seeds (*Trigonella foenum-graecum*) are widely studied for their potent antidiabetic and ovulatory benefits, making them a promising herbal intervention for PCOD. The active constituent 4-hydroxyisoleucine, a exceptional amino acid derivative, has a critical role in enhancing insulin receptor activity, thereby reducing hyperinsulinemia, a key trigger of androgen excess and menstrual dysfunction in PCOD. Clinical studies have confirmed that fenugreek supplementation leads to restoration of ovulation, reduction in ovarian cyst size, and improvement in insulin resistance markers such as HOMA-IR. Additionally, diosgenin, a steroidal saponin present in fenugreek, mimics estrogen and stimulates follicular development, promoting more regular menstrual cycles. Fenugreek also exhibits anti-inflammatory, hypolipidemic, and hepatoprotective potential, making it an effective multi-targeted agent in addressing the metabolic and reproductive aspects of PCOD.[6]

C. Nigella sativa: anti-inflammatory and anti-androgenic effects

Nigella sativa, commonly referred to as black seed or kalonji, possesses a highly bioactive compound called thymoquinone, which demonstrates powerful anti-inflammatory, antioxidant, and anti-androgenic properties. In PCOD, where continuing low-grade inflammation and elevated androgens are prevalent, thymoquinone downregulates proinflammatory cytokines such as TNF-α and interleukin-6 and prevents enzymes involved in androgen biosynthesis like 5α-reductase and 17β-HSD. Several clinical trials have shown that Nigella sativa usage can reduce serum testosterone, recover menstrual regularity, and enhance insulin sensitivity.[7] Furthermore, it has been linked to developments in lipid outlines, liver function, and body weight all of which are commonly impaired in PCOD. Its adaptogenic and immunomodulatory actions further support endocrine balance, making it a potent herbal ally in the comprehensive treatment of PCOD.

D. Chia seeds: omega-3 and lipid control

Chia seeds (*Salvia hispanica*) are a nutritional powerhouse containing high levels of alpha-linolenic acid (ALA), soluble fiber, magnesium, and calcium, all of which contribute to the metabolic regulation of PCOD. ALA, an omega-3 fatty acid, has been shown to decrease the expression of proinflammatory markers and advance insulin sensitivity, key factors in both the metabolic and reproductive symptoms of PCOD.[8] The soluble fiber content supports blood sugar regulation, slows gastric emptying, and aids in appetite control, making chia seeds particularly effective for weight management. Moreover, chia seeds help recover lipid profiles by reducing low density level cholesterol and promoting high density level cholesterol, thereby mitigating cardiovascular risks often associated with PCOD. While they do not exert direct hormonal modulation like flax or fenugreek, their anti-inflammatory and metabolic benefits provide foundational support in integrative PCOD management.

E. Pumpkin and sunflower: nutrient synergy in seed cycling

Pumpkin (*Cucurbita pepo*) and sunflower (*Helianthus annuus*) seeds are integral to the practice of seed cycling, a naturopathic method that involves rotating specific seeds according to the stages of the menstrual cycle to help hormonal synchronization. Pumpkin seeds are high in zinc, which has a essential role in supporting progesterone production and ovulation by modifiable the hypothalamic-pituitary-ovarian axis. Zinc also reduces androgenic effects and supports follicular development. Sunflower seeds, on the other hand, are rich in selenium, a potent antioxidant that aids in liver detoxification of excess estrogen, and vitamin E, which supports luteal phase function and reduces premenstrual symptoms. When used in tandem during various stages of the cycle (pumpkin and flax in the follicular phase; sunflower and sesame in the luteal phase), these seeds help balance estrogen and progesterone, regulate cycles, and support reproductive health. Though scientific validation of seed cycling is limited, the individual content in these seeds is well-supported by research in hormonal regulation and oxidative stress reduction.[9]

Mechanisms of action

a. Endocrine modulation

Endocrine modulation refers to the process by which substances (such as drugs, hormones, or other bioactive compounds) interact with and alter the normal functioning of the endocrine system. The endocrine system is composed of glands that produce hormones into the bloodstream, which act on various tissues to regulate purposes such as metabolism, growth, reproduction, and mood. Compounds can influence the synthesis or secretion of specific hormones. For example, some drugs can enhance or inhibit the release of insulin from the pancreas or thyroid hormones from the thyroid gland. Hormones employ their properties by binding to specific receptors, which are often situated on the surface of target cells. Endocrine modulators can mimic or block these hormonal actions by binding to receptors. For example, selective estrogen receptor modulators (SERMs) bind to estrogen receptors and can either activate or inhibit estrogenic effects specific on the tissue. Hormone-receptor binding often triggers a cascade of intracellular signaling pathways that lead to physiological changes in the

cell, such as changes in gene expression or protein synthesis. Drugs or compounds can modulate these pathways either by enhancing or inhibiting the signaling. The degradation of hormones, typically by enzymes such as cytochrome P450 or proteolytic enzymes, can be accelerated or inhibited by endocrine modulators, affecting the half-life and potency of circulating hormones.[10]

b. Anti-inflammatory pathways

Inflammation is an inbuilt resistance mechanism of the body that helps to eliminate harmful stimuli, such as pathogens or injury, and initiate the healing process. However, chronic inflammation is associated with a variety of ailments such as arthritis, cardiovascular disease, and cancer. Anti-inflammatory pathways refer to the mechanisms through which compounds reduce or suppress inflammation. Cyclooxygenases (COX-1 and COX-2) are enzymes intricated in the making of prostaglandins, which are lipid mediators of inflammation. Non-steroidal anti-inflammatory drugs, such as aspirin and ibuprofen, hinder COX enzymes, leading to reduced prostaglandin production and diminished inflammation. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) is a main actuator of inflammation. Inflammatory stimuli activate NF-kB cell, which transports to the nucleus and activates the transcription of pro-inflammatory cytokines and other immune mediators. Anti-inflammatory drugs can inhibit the NF-kB pathway, thus reducing the production of inflammatory cytokines such as TNF-α, IL-1, and IL-6. The mitogen-activated protein kinase (MAPK) signaling pathway is another key player in inflammation. This pathway is activated by various pro-inflammatory cytokines and mediators. MAPK inhibitors can reduce the expression of inflammatory mediators by preventing the initiation of transcription factors like AP-1 and NF-kB. Anti-inflammatory compounds can also act directly on pro-inflammatory cytokines. For instance, corticosteroids and biologic agents like TNF-α inhibitors block the signaling of specific cytokines involved in inflammation. Inflammasomes are multiprotein complexes involved in the initiation of pro-inflammatory cytokines such as IL-1β and IL-18. Some anti-inflammatory agents inhibit inflammasome activation, thus reducing the secretion of these cytokines. The activation of the endocannabinoid system, particularly through the CB2 receptor, has been known to employ anti-inflammatory properties by modulating immune cell responses.[11]

c. Antioxidant properties

Antioxidants are molecules that neutralize free radicals or reactive oxygen species (ROS), which are extremely reactive molecules that can harm cellular structures, with DNA, proteins, and lipids. The body has a range of antioxidant defenses, but external antioxidants from food or supplementation can help reduce oxidative stress. Antioxidants directly neutralize ROS by donating an electron to stabilize the free radical. Common antioxidants include vitamins such as Vitamin C, Vitamin E, and polyphenols from plant-based foods, as well as enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase.[12] Some compounds induce the production of endogenous antioxidant enzymes. For example, compounds such as curcumin or sulforaphane can stimulate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, resulting to the increased expression of antioxidant enzymes like SOD, catalase, and heme

oxygenase-1. ROS can be generated through the interaction of transition metals (such as iron and copper) with oxygen. Antioxidants can chelate these metals, preventing them from participating in ROS-producing reactions (e.g., Fenton reaction). Certain antioxidants have been shown to assist in the restoration of oxidative impairment. For example, polyphenols can activate DNA repair pathways that counteract oxidative DNA damage.

d. Insulin receptor sensitization

Insulin receptor sensitization refers to the process through which compounds improve the body's response to insulin, thereby enhancing its capability to control blood glucose levels. This is particularly important in conditions like type 2 diabetes, where insulin resistance occurs. AMPK is a key regulator of cellular energy balance. When activated, AMPK encourages glucose uptake and consumption, while also improving insulin sensitivity. Several compounds, including metformin, activate AMPK to improve insulin sensitivity. Chronic low-grade inflammation is a main regulator of insulin resistance. By modulating inflammatory pathways (e.g., NF-kB, TNF-α), insulin receptor sensitizers reduce systemic inflammation, thereby improving insulin signaling. Adipose tissue releases various signaling molecules (adipokines) like leptin, adiponectin, and resistin. Insulin resistance is often associated with an imbalance in these adipokines. Insulin receptor sensitizers can promote the secretion of adiponectin (which enhances insulin sensitivity) and reduce resistin (which contributes to insulin resistance). Some compounds directly enhance the activity of the insulin receptor. For example, thiazolidinediones (TZDs) trigger peroxisome proliferator-activated receptor gamma (PPAR-γ), which improves insulin sensitivity by increasing the expression of genes involved in glucose and lipid metabolism. Lipotoxicity (the accumulation of fatty acids in tissues such as the liver and muscles) is a major contributor to insulin resistance. Some insulin sensitizers help reduce lipid accumulation or improve the oxidation of fatty acids, thereby enhancing insulin sensitivity.[13] Impaired mitochondrial function is associated with insulin resistance. By improving mitochondrial activity and energy metabolism, some compounds can enhance insulin sensitivity.

Formulation strategies and dosage forms

The development of effective dosage forms is critical in the delivery of bioactive compounds, especially those derived from herbal sources, to ensure their efficacy, stability, and bioavailability. Various formulation strategies are employed to optimize the therapeutic potential of plant-based remedies and natural products.

- Herbal Decoctions: Herbal decoctions are liquid preparations made by boiling plant materials (roots, stems, leaves, or bark) to extract their active constituents. These are typically used for medicinal herbs with water-soluble compounds that require extraction through heat and long boiling periods. Decoctions are often used for their therapeutic properties in conditions like digestive disorders, respiratory issues, and inflammatory diseases. While herbal decoctions can be highly potent, they can also be challenging to standardize, and issues such as variability in plant source and extraction methods may affect their consistency. One of the key considerations in formulating decoctions is ensuring that the plant material is of high quality and free from contaminants.

- Capsules and Seed Oils: Capsules are one of the most commonly used dosage forms for herbal products because they offer precise dosing, stability, and ease of use. In this form, powdered herbs, oils, or extracts are encapsulated in gelatin or vegetarian capsules. For example, omega-3-rich seed oils, such as flaxseed or chia oil, are commonly formulated into soft gel capsules. These oils offer health aids such as anti-inflammatory and cardiovascular support. Encapsulation also protects the contents from light, oxygen, and moisture, helping preserve their bioactivity. Seed oils are often concentrated and provide a convenient and standardized way of delivering specific therapeutic doses of bioactive compounds like polyunsaturated fatty acids (PUFAs).
- Seed Powders and Dietary Incorporation: Another formulation strategy is the use of seed powders, which can be directly incorporated into the diet or encapsulated into convenient forms. Seeds such as flaxseeds, chia seeds, and pumpkin seeds are loaded with essential fatty acids, fiber, and antioxidants. They can be ground into powder and included in smoothies, baked goods, or as a topping for various dishes. This approach offers an easy and accessible method of incorporating herbal or seed-based nutrition into daily dietary routines. The powders can be processed in a way that preserves nutrients while ensuring that their therapeutic benefits are maintained. Dietary incorporation is particularly useful for chronic conditions where long-term use and adherence are essential.[14]

Safety, toxicity & contraindications

The safety of herbal formulations and natural products is a crucial aspect of their clinical use. While many herbal products offer therapeutic benefits, they must be evaluated for potential toxicity and adverse effects, especially when used over extended periods or in mixture with other medications. Herbal products can interrelate with prescription medications, possibly dropping their efficacy or producing detrimental side effects. For instance, St. John's Wort, a well-known herbal preparation for depression, can relate with several drugs, including oral contraceptives, anticoagulants, and antidepressants, by affecting liver enzymes (particularly CYP450) that metabolize these drugs. Similarly, garlic and ginger can improve the properties of blood thinners like warfarin, growing the risk of bleeding.[15] Therefore, it is important for healthcare providers to carefully monitor patients who are taking both herbal supplements and prescription medications, ensuring there are no dangerous interactions. The appropriate dosage of herbal supplements varies according to the specific plant or compound, the form of the product (e.g., powder, capsule, decoction), and the intended therapeutic use. Herbal formulations should be standardized for their active ingredients to ensure consistent dosing and effectiveness. For example, standardized extracts of ginseng or curcumin are often recommended at doses of 200-400 mg per day. However, precise dosing is sometimes difficult due to the variability in the potency of plant materials. Adherence to recommended dosages based on clinical guidelines or pharmacological studies is critical for minimizing the risk of adverse effects. Reproductive safety is an important consideration when using herbal products, especially during pregnancy, lactation, or in individuals planning to conceive. Some herbs may cause uterine contractions, alter hormone levels, or affect fetal development. For example, herbal products like black cohosh or

dong quai, which are sometimes used to alleviate menopausal symptoms, may not be safe during pregnancy.[16] Similarly, high doses of Vitamin A or herbs like licorice have been associated with potential risks during pregnancy. Therefore, it is vital to assess the safety of specific herbs in reproductive health, and pregnant or lactating individuals should avoid using herbal products unless prescribed by a healthcare professional.

Future prospects and research gaps

Despite the increasing attention in herbal and natural formulations, there are several areas in which further research is needed to confirm the safe and actual use of these products in clinical settings. While preclinical studies and small-scale clinical trials have given appreciable information regarding the benefits of herbal remedies and natural compounds, large-scale randomized controlled trials are still lacking for many herbal products. These trials are necessary to create ultimate evidence of efficacy, safety, and optimal dosing, particularly for chronic diseases such as diabetes, cancer, and cardiovascular disease. Large-scale trials can also help identify specific patient populations that may benefit most from herbal treatments and clarify the role of herbal medicine in integrative healthcare. A deeper data of the molecular devices underlying the actions of herbal compounds is essential for optimizing their use. Advances in systems biology and molecular pharmacology, including transcriptomics, proteomics, and metabolomics, can help elucidate how herbal products interact with cellular and molecular pathways. By identifying the precise targets and mechanisms of action, researchers can develop more effective formulations and improve patient outcomes. For example, molecular approaches can clarify how compounds like curcumin, quercetin, or resveratrol influence cellular signaling pathways related to inflammation, oxidative stress, or apoptosis.[17] Nutrigenomics, the study of how nutrition and bioactive compounds influence gene expression and health outcomes, represents an exciting frontier in herbal medicine research. Understanding how herbal products can interact with an individual's genetic makeup can provide insights into personalized medicine. For example, certain herbal compounds may be more effective in individuals with specific genetic polymorphisms related to drug metabolism or inflammatory pathways. This approach can pave the way for tailored herbal interventions that optimize efficacy and minimize side effects**.**

Conclusion:

Herbal formulations, including decoctions, capsules, oils, and seed powders, represent a promising and natural approach to health and wellness. They provide a diverse choice of therapeutic aids, such as anti-inflammatory, antioxidant, and insulin-sensitizing effects. However, despite their widespread use, the safety, efficacy, and optimal dosages of many herbal products require further investigation, particularly in large-scale clinical trials. Additionally, understanding the molecular and genetic mechanisms behind their effects through systems biology and nutrigenomics will enhance the precision and personalization of herbal medicine. As study continues to progress, it is essential to bridge the gaps in knowledge regarding interactions with medications, reproductive safety, and long-term toxicity to ensure that these natural remedies can be used carefully and successfully in clinical training.

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JACKFRUIT AND ITS POSITIVE EFFECTS ON HEALTH

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Abstract:

Jackfruit, scientifically known as *Artocarpus heterophyllus* Lam., is an underappreciated fruit that packs a nutritious punch in both its edible and non-edible byproducts. In spite of their reputation as a food waste product, jackfruit seeds are actually quite nutritious, with a wealth of protein, carbohydrates, and bioactive chemicals. Phenolics such as gallic acid, catechin, epicatechin, rutin, and ferulic acid are among the bioactive components that have numerous health-promoting qualities. By lowering free radical formation, these bioactive chemicals lessen the risk of different diseases. They also possess numerous pharmacological activities and a strong antioxidant capacity. The addition of jackfruit seed flour to the created product will boost its protein content and aid in the valorisation of trash. The starch that is removed from jackfruit seeds has several possible uses, including in the pharmaceutical business, but it can also be used as a thickening, gelling agent, or filler. In light of this, the review places an emphasis on jackfruit's nutritional profile, health advantages, and relevant product formulation uses. Regarding the nutritional components, our main focus is on studying starch extraction methods and its functional qualities as they pertain to industrial uses. So, to provide a thorough overview of the jackfruit seeds' potential for the food business, this review will integrate the findings.

Keywords: Jackfruit, Nutritional Value, Antioxidant, Anti Diabetic.

Introduction:

Native to India, the jackfruit tree (*Artocarpus heterophyllus* Lam.) ranks among the tallest fruit trees in the world. Traditional wisdom held that the jackfruit tree first appeared in the Western Ghats rainforest. Various regions of South America, Africa, and Asia are home to this tropical fruit, which is a member of the Moraceae family. The jackfruit has several purposes, including as a source of nutrition, fuel, lumber, fodder, and medicine. In its early years, *Artocarpus heterophyllus* can grow 1.5 m/year in height; but, as it matures, its growth rate slows to approximately 0.5 m/year. The seeds of this fruit, which are typically discarded, can be round, oval, or spheroid in shape, and can be anywhere from 1.5 to 2.5 cm thick and 2-4 cm long. The high carbohydrate and protein content of the seeds—which can number anywhere from 100 to 400 per fruit—accounts for about 11 to 15% of the fruit's overall weight.[1-3] According to research, jackfruit seeds contain a wealth of nutrients, including carbs (25.80-38.40 g), protein (0.40-0.43 g), fat (0.40-0.43 g), crude fiber (1.0-1.5 g), vitamin A (10-17 IU), vitamin C (11 mg), calcium (50.0 mg), potassium (246 mg), magnesium (54.0 mg), and iron (1.50 mg) per 100 g on a fresh weight or FW basis.[4] Despite their many health benefits and abundance of bioactive

substances like tannins, caffeic acid, ferulic acid, gallic acid, and polyphenols, this fruit is underappreciated in India compared to others because of the excessive amount of waste it produces. The best time to get jackfruit seeds is between March and July because the fruit is very seasonal.[5] The amount of waste produced by jackfruit is unparalleled by any other fruit. Kerala loses 2,000 million jackfruit seeds every year, while Karnataka loses 35,000 million seeds per year, according to a new study.[6] The seeds, perianths, and peel or rind of this fruit are its most common byproducts. There has been very little scientific investigation of jackfruit, despite the fact that it has many culinary uses and is rich in health benefits. Along with phytonutrients like lignans, isoflavones, and saponins, jackfruit seeds are a great way to get the protein and carbs you need, and they also have anti-cancer, anti-aging and antioxidant properties. For conditions like cancer, high blood pressure, ulcers, nerve function, asthma, and more, some studies have shown promise in using the seeds. According to Swami *et al.* (2007), antioxidants like selenium, β-carotene, α-lipoic acid, vitamin A, vitamin C, and vitamin E can aid in the treatment of coronary heart disease, hypertension, lung cancer, and prostate cancer.

The high nutritional value of the seeds makes them suitable for processing or incorporation into other foods, and they are discarded in significant quantities after product production. The antinutrient content of seeds can be diminished through a variety of pre-treatments, including as boiling, autoclaving, germination, roasting, and so on. Additionally, by turning seeds into flour, they may be added to a variety of items, making them more functional. The nutritional composition and functional characteristics of jackfruit seeds and seed powders have been the subject of much research. Nevertheless, there is a lack of centralized records that compare various approaches to reducing antinutritional factors and enhancing their functioning for product development. The nutritional and chemical content of extracted starch is another area that this review intends to cover. Its primary focus is on starch extraction methods and the functional qualities of extracted starch as they pertain to seed applications in industry. So, to provide a thorough assessment of the possibilities of jackfruit seed valorisation for the food business, this review will compile the results.[8]

Health benefits of jackfruit

The medicinal and physiological properties of jackfruit have made them a hot topic in recent years.[9] Jackfruit and its seeds have several medical uses due to the abundance of vital minerals and bioactive chemicals they contain. The potential of nanoparticles made from jackfruit seeds as antimicrobial agents was highlighted by a study by Theivasanthi *et al.* (2011), which showed that they were highly efficient against *Bacillus megaterium* and *Escherichia coli*.[10] According to the study, the antibacterial activity of jackfruit seed nanoparticles is greatly enhanced by their specific surface area (SSA). A higher SSA increases contact with bacterial cell walls, which in turn increases the potency of antimicrobial actions, hence this is of utmost importance.

The seeds of the jackfruit fruit have great potential as a medicinal agent that can fight off bacterial illnesses and even work as a shield against food-borne diseases in food processing

facilities. The jackfruit seeds have two uses: as a nutritional component and as a natural antibiotic. This makes them a potential ingredient in nutraceuticals and functional foods. Additionally, studies on the SSA of different bacterial strains corroborate the idea that surface area plays a major role in how antimicrobial agents interact with bacterial cells. With this new information, we can better comprehend the potential mechanisms by which nanoparticles derived from jackfruit seeds can exert their antibacterial properties.

Jackfruit seeds have several uses in the food business in addition to their therapeutic ones. As an example, jackfruit seed flour's outstanding thickening and binding capabilities have made it a promising functional component. Because of its antibacterial properties and capacity to improve texture and stability, it is well-suited for use in a wide range of food products.[11] Thus, using jackfruit seeds is a fresh take on a long-standing problem: how to make food safer, promote sustainability, and alleviate public health worries about infectious diseases.

Digestion/immune deficiency

The nutritional and therapeutic significance of jackfruit seeds has long been recognized by many cultures. They are an important part of herbal antidotes in India that help those who drink too much, and they have a reputation for reducing alcohol's harmful effects in China.[12] The high concentration of antioxidant, anti-inflammatory, and hormone-regulating phytonutrients in seeds lend credence to these age-old uses. These phytonutrients include lignans, saponins, and isoflavones. The health benefits of the seeds are enhanced by these bioactive chemicals.

Another interesting finding is that deep-fried foods made with jackfruit seed flour have a lower absorption of fat. This could be a step towards creating healthier food options. Efforts to combat diet-related health problems, such obesity and cardiovascular diseases, may find this attribute very useful. Essential trace minerals, such as magnesium and manganese, are present in jackfruit seed powder, according to nutritional research. These elements are crucial for enzyme activity, bone health, and metabolic functions.

The seeds of the jackfruit fruit are rich in nutrients and also include the lectins jacalin and artocarpin. The biological applications of these carbohydrate-binding proteins seem promising. Particularly in the assessment of immune state in individuals infected with Human Immunodeficiency Virus type 1 (HIV-1),[13] jacalin has been utilized as a biochemical instrument in immunological studies. It finds value in diagnostic and therapeutic settings due to its selectivity for binding to certain glycoproteins. The antibacterial and anticancer activities of artocarpin have been shown in multiple experimental experiments, adding credence to the therapeutic value of jackfruit seeds.

The results indicate that jackfruit seeds contain chemicals with various health advantages and are also nutrient-rich byproducts. Particularly in areas where functional foods and traditional medicine are important, their incorporation into therapeutic and dietary practices has the potential to improve public health.

Vitamin a deficiency/inflammation

The medicinal potential of jackfruit seed flour and starch has recently come to the forefront, thanks to the bioactive components found in them, such as the lectin jacalin. The secondary metabolite jacalin, which is present in jackfruit seeds, possesses anti-angiogenic and anti-inflammatory characteristics, which make it an attractive option for managing inflammation. Novel formulations, like fat-dissolving tablets, have resulted from the use of jackfruit seed-derived components in pharmaceutical applications. As an all-natural, plant-based substitute for synthetic excipients, these pills make use of the high carbohydrate and protein content found in jackfruit seed cotyledons.

Jackfruit seed starch has recently come to light as a potential pharmaceutical industry ingredient, particularly for the creation of fast-dissolving tablets (FDTs). The seed starch works well as a superdisintegrant, which means it helps the pills break down quickly when they come into touch with saliva or stomach acid, increasing the amount of active medicine that is absorbed into the bloodstream. Patients who have difficulty swallowing regular tablets, such as those who are young, elderly, or dysphagic, may benefit greatly from this application in formulations made for them.

Jackfruit seeds are an excellent source of carbohydrate and many other phytoconstituents. Complex starches, natural sugars, and fiber are all examples of carbs. Iron, magnesium, phosphorus, potassium, sodium, and calcium are just a few of the minerals included in these foods. These elements are vital for many bodily processes. The volatile chemicals found in jackfruit seeds, such as isopentyl isovalerate, butyl isovalerate, and butyl acetate, are responsible for their unique smell and may have bioactive properties. Additionally, lectins like jacalin lend credence to their medicinal importance, especially in the fields of immunology and anti-cancer studies.

Jackfruit has been linked to better digestive health due to its high fiber content (around 3.6 g per 100 g). Shedge *et al.* (2012) states that this high fiber intake aids in maintaining regular bowel movements and promotes smooth bowel movements.[14] According to Swami *et al.* (2012), the fiber also helps remove any carcinogens from the large intestine, which protects the colonic mucosa. Jackfruit seed derivatives have the ability to be used as functional food ingredients that have both nutritional and medicinal effects. Their dual role in supporting digestion and preventing cancer further highlights this possibility.[15]

Diabetes

The seeds are a great source of B-complex vitamins and can aid with weight loss, prevent constipation, lower the risk of cardiovascular disease, and more. According to research by Maurya and Mogra, (2016), the starch in jackfruit seed flour aids in bowel health and glucose regulation.[16] It also has antimicrobial qualities, which could prevent food poisoning. Furthermore, it was asserted that the seeds' magnesium content could potentially lower blood pressure and maintain bone health through improved calcium absorption. Phytoconstituents found in jackfruit seeds include sugar, starch, and dietary fiber, as well as minerals like calcium,

magnesium, phosphorus, potassium, salt, and iron. Similarly, Thatsanasuwan *et al.* (2023) found that diabetic pasta had jackfruit seed flour (120 g) in addition to millet, which increased the consumption of protein, carbohydrates, and fiber. There is a lot of highly soluble protein in the seeds, which aids with stress and anxiety management. Obesity can be prevented by eating these seeds because of their reduced ability to absorb water and fat. Additionally, it protects against colon cancer, protects the body from electrolyte imbalances and flavonoids, keeps blood pressure normal, reduces the danger of blood clots, and lowers the toxic effect in the colon.[17.18]

Other Uses

The use of non-traditional starch sources in manufacturing has gained more attention in recent years. Consequently, jackfruit seeds have attracted a lot of interest from academics due to their high starch content.[19] The starch content of jackfruit seeds is high—about 20% (dry basis)—and according to research by Tulyathan *et al.* (2002)[20], the starch recovery yield from jackfruit seeds was around 77%. This suggests that jackfruit seeds could be a useful starch source for the food and pharmaceutical industries [21], as well as a thickener, binding agent, and stabilizer.[22] One great technique to make more use of fresh seeds is to grind them into flour.

Rengsutthi and Charoenrein, (2011) looked into the prospect of thickening and stabilizing chili sauce with jackfruit seed starch. It was discovered that jackfruit seed starch, when added to chili sauce at a concentration of 1%, may stabilize the pH, titratable acidity, and total soluble solids. In comparison to chili sauce made using maize starch, the study found that chili sauce made with jackfruit seed starch had better quality. Combining 11% jackfruit seed flour with 27% dried jackfruit pulp results in cereal bars that are high in nutritional value and have a pleasant texture and flavour.[22,23]

The high concentration of non-reducing carbohydrates in jackfruit seed makes it an ideal candidate for prebiotic use.[24] For the extracellular synthesis of pullulan by Aureobasidium pullulans MTCC2195[25] and polyhydroxybutyrate by Bacillus sphaericus NCIM 5149[26], jackfruit seed has been used as a carbon source in multiple experiments with positive results. Nair *et al.* (2017) sought to add value to an agricultural byproduct by biotechnologically producing L-lactic acid from jackfruit seed powder using *Streptococcus equinus*.[27]

Researchers looked at the potential of using jackfruit seed starch powder in irbesartan fast-dissolving tablets as a new kind of natural super disintegrant.[28] The seeds of five distinct jackfruit cultivars were used by Nagala *et al.* (2013) to extract oils that included antioxidant activity and necessary fatty acids.[29]

The high protein content of jackfruit seeds makes them a promising raw material for ethanol synthesis, which might be seen as a renewable energy source and a protein source in the food business.[30,31] Utilizing jackfruit peel for pectin production can add to the economic development of jackfruit-growing regions by increasing income for processors and farmers and decreasing wasteful effects on the environment. Jackfruit peel is rich in fibrous compounds and pectin, among other nutrients. The effect of various extraction procedures on the yield, physicochemical and structural aspects of pectin obtained from jackfruit waste was

investigated.[32] Further research is needed to increase the solubility of the recovered pectin from jackfruit waste in order to produce pectin of higher quality, as it was inferior to commercial pectin due to its high ash content and poor solubility. Therefore, a number of studies have concentrated on improving upon traditional methods of pectin extraction from jackfruit peel by employing more modern approaches, such as ultrasonic-microwave assisted extraction and ultrasound assisted extraction, which both yielded larger amounts of pectin. The potential use of pectin obtained from jackfruit peel in bone healing applications was highlighted in earlier report.[33]

The economic value of jackfruit peel has been investigated, and it has been found to be suitable for use as an efficient raw precursor for the production of activated carbon using various techniques like microwave induced NaOH activation and phosphoric acid activation.[34] This research aims to reduce the cost of waste disposal, increase the availability of a potentially inexpensive raw material for commercial scale activated carbon production, and ultimately prevent deforestation by reducing the utilization of wood for activated carbon production. To make bio oil, another viable substitute for non-renewable fossil fuels, jackfruit peel is utilized.[35] In an effort to find new uses for these materials, Ashok *et al.* (2018) investigated the possibility of creating a dye-sensitized solar cell with a natural photo-sensitizer derived from jackfruit rags.[36] Artocarpin, a protease isolated from jackfruit latex that exhibited proteolytic activity against casein, was isolated and purified shown in previous study.[37] You can also use the jackfruit latex as an adhesive. Researchers from Sri Lanka's Department of Food Science and Technology at the University of Sri Jayewardenepura looked at the nutritional value of jackfruit stalks in an unpublished study. In an effort to increase jackfruit consumption, all these studies show that jackfruit might be used commercially.

Conclusion:

A tropical tree, the jackfruit provides an abundant source of several nutrients, including carbohydrates, proteins, vitamins, minerals, dietary fiber, and phytochemicals. It is a tree that grows in tropical regions. Jackfruit has been shown to have several health benefits, including anticarcinogenic, antibacterial, antifungal, anti-inflammatory, wound healing, and hypoglycemic qualities, according to research that were conducted in the past. On the other hand, it is considered to be an underutilized fruit on a commercial scale. This is primarily due to the fact that it contains a higher percentage of inedible proportions, which results in an increased amount of waste. Additionally, it is difficult to peel and separate edible bulbs from the rind, there is a lack of knowledge regarding appropriate postharvest practices, and there are insufficient processing facilities in regions where they are grown. Therefore, adhering to correct postharvest practices and converting jackfruit into products that have undergone minimal processing, such as pre-cut jackfruit, may encourage a greater number of people to consume jackfruit. Additionally, the conversion of jackfruit waste materials into valuable products may assist in the management of waste. There have only been a few of research conducted in recent times that have concentrated on increasing the shelf life of jackfruit and adding value to jackfruit trash by

turning it into a variety of goods and renewable energy sources. Therefore, there should be a greater emphasis placed on doing research in order to identify potential industrial applications of jackfruit and to ensure that waste generated during the processing of jackfruit is properly managed.

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ROSEMARY (*SALVIA ROSMARINUS*): A PHYTOCHEMICAL AND PHARMACOLOGICAL OVERVIEW

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Abstract:

Salvia rosmarinus (formerly Rosemary, or *Rosmarinus officinalis L.*, is a fragrant perennial plant that is a member of the Lamiaceae family. Originating in the Mediterranean region, it is currently grown all over the world, rosemary has garnered substantial scientific attention due to its rich phytochemical composition and diverse pharmacological activities. Traditionally used in culinary and folkloric medicine, rosemary is increasingly valued in pharmaceutical, nutraceutical, and cosmetic industries for its antioxidant, antimicrobial, AIA (anti-inflammatory) & neuroprotective property. Rosemary's therapeutic potential is primarily attributed to a combination of volatile and non-volatile bioactive compounds. Its essential oil collected mostly from the blooming tops and greenery using steam distillation, contains major constituents such as 1,8-cineole (eucalyptol), α-pinene, borneol, camphor and verbenone. The monoterpenes and diterpenes exert significant biological effects, including bronchodilation, analgesia, antimicrobial action, and AIA (anti-inflammatory activity) by the suppression of cytokines like TNF-α & IL-1β. Additionally, verbenone and 1,8-cineole have shown potential in neuroprotective applications, including the management of cognitive impairments like Alzheimer's. The non-volatile ingredients in rosemary, especially the phenolic compounds carnosic acid, rosmarinic acid, carnosol are strong antioxidants that can reduce reactive oxygen species (ROS) and improve endogenous antioxidant enzyme systems, including glutathione peroxidase and superoxide dismutase. These compounds also exert anti-inflammatory and anticancer impacts by adjusting important signaling pathways like PI3K/Akt /NF-κB /MAPK, making them relevant in relation to persistent medical conditions, including neurodegenerative & oncological. The flavonoid content of rosemary, notably apigenin, luteolin, and genkwanin, adds further depth to its pharmacological profile. These compounds display strong anti-inflammatory and antioxidant activities and have shown promise in cancer prevention and cognitive health. Apigenin and luteolin, for example, inhibit COX-2 and pro-inflammatory cytokines while encouraging cell cycle arrest and apoptosis in different cancer cell line. Their ability to cross BBB (blood-brain barrier) positions it as potential candidates towards neurodegenerative disease management. Triterpenes such as ursolic acid and oleanolic acid, though present in smaller

amounts, contribute hepatoprotective, anticancer, and anti-inflammatory properties. These triterpenes act by inhibiting pro-inflammatory mediators and enhancing cellular antioxidant defenses. Collectively, the synergistic interaction of essential oils, phenolics, flavonoids, and triterpenes defines the herb rosemary serving many purposes and has a wide range of medicinal uses. Given the breadth, its pharmacological actions, rosemary continues to attract interest for integration into evidence-based medicine. However, while preclinical studies are promising, to establish standardized dosages, safe profiles, therapeutic efficiency in human populations, testing is essential. Overall, *Salvia rosmarinus* stands out as a botanically and pharmacologically significant species with far-reaching implications for healthcare, wellness, and functional food development.

Keywords: *Salvia rosmarinus*, Essential Oils, Antioxidant, Neuroprotective, Anti-Inflammatory.

Introduction:

The thorny, perennial, fragrant plant known as rosemary (*Salvia rosmarinus*, formerly *Rosmarinus officinalis L.*) belongs to the Lamiaceae family. Widely recognized for its culinary uses, rosemary has also attracted extensive scientific curiosity because to its strong pharmacological characteristics, particularly antimicrobial, AIA (anti-inflammatory) and antioxidant effects. Originally from the Mediterranean area, now cultivated globally & forms an important resource in the pharmaceutical, food, and cosmetic industries.

Biological source

Botanically, rosemary is classified as:

- Kingdom: Plantae
- Clade: Angiosperms
- Order: Lamiales
- Family: Lamiaceae
- Genus: *Salvia*
- Species: *Salvia rosmarinus* (formerly *Rosmarinus officinalis* L.)

Rosemary a hardy, drought-resistant bush that is capable of reaching a height of 1.5 meters. The underside of the leaves is white-hairy, while the upper surface is dark green linear & needle-like, with a distinctive aromatic smell due to the presence of essential oils. The plant produces pale blue to purple flowers that bloom primarily in spring and are highly attractive to pollinators like bees and butterflies. The essential oil, responsible for the plant's therapeutic value, is primarily removed by steam distillation from the leaves and blooming tops.[1]

Geographical distribution

Native eange

Rosemary is indigenous to the Mediterranean basin, particularly thriving in regions of countries like Italy, France, Spain, Turkey, Greece & North African nations like Morocco and Algeria. These regions provide optimal conditions—dry, rocky soils and ample sunlight—that support rosemary’s robust growth. [2]

Global cultivation

Due to its economic and medicinal significance, rosemary is now cultivated in many regions beyond its native range. These include:

- Europe: Especially prevalent in southern countries such as Italy, Spain, and Portugal, where it is farmed for essential oil production and culinary use.
- Asia: Grown in India, especially in the Himalayan foothills, where the temperate climate supports good yields.
- Americas: Commercially cultivated in the United States (California), Mexico, and Brazil, with increasing interest in essential oil markets.
- Africa: Extensively grown in North African countries such as Egypt and Morocco, contributing significantly to the export of rosemary essential oil.

Rosemary thrives in Mediterranean-type climates with well-drained soil, moderate to warm temperatures, and plenty of sunlight. While the plant can grow wild in coastal and mountainous areas, most commercial production is conducted under controlled agricultural conditions to ensure consistent phytochemical quality.

Rosemary can adapt to a variety of environmental conditions, though it thrives best in Mediterranean-like climates. It is also found growing wild on coastal cliffs and rocky hillsides.

Chemical composition

The pharmacological properties of rosemary is mainly because of its complex phytochemical profile. Its chemical composition varies depending on geographical origin, climatic conditions, harvesting time, and extraction method.

1. Essential oils

The essential oil content of *Rosmarinus officinalis* (now classified as *Salvia rosmarinus*) varies from 1% to 2.5%, based on a number of variables, including the plant's location, harvest season, and extraction method. The oil is obtained primarily by steam distillation from the leaves and blooming tips. Rosemary essential oil is a complex mixture predominantly composed of monoterpenes and diterpenes, which are responsible for its characteristic aroma and various pharmacological properties.[3,4]

1,8-Cineole (Eucalyptol): One of the main ingredients of rosemary essential oil is 1,8-cineole, sometimes referred to as eucalyptol, often comprising 20–50% of the oil. It is a monoterpene oxide known for its camphor-like odor and anti-inflammatory, expectorant, and bronchodilator effects. 1,8-Cineole enhances mucociliary clearance, making it beneficial for respiratory conditions including bronchitis and asthma. It also highlights its potential as a natural anti-inflammatory drug by inhibiting the production of inflammatory cytokines including TNF-α and IL-1β. [5]

Camphor: Camphor is a monoterpene ketone present in rosemary essential oil in concentrations ranging from 5–20%. It possesses analgesic, antimicrobial, and counterirritant properties. Topically, camphor is used in pain-relieving balms due to its ability to stimulate nerve endings, creating a cooling sensation followed by warmth. Additionally, it has shown broad-spectrum

antibacterial action, particularly against Staphylococcus aureus and other Gram-positive bacteria. [6] However, because high amounts of camphor can be neurotoxic, it should be taken with caution.

α-Pinene: α-Pinene is a bicyclic monoterpene hydrocarbon that imparts a pine-like aroma which becomes characteristic for essential oil of rosemary. It is known of its AIA (anti-inflammatory), bronchodilator properties & antioxidant activity. α-Pinene reduce inflammation by inhibiting COX-2 and NF-κB activation. It has also shown antimicrobial and antitumor activity in vitro. [7] α-Pinene's ability to cross the BBB depicts potential for neuroprotective & cognitive-enhancing effects. [8]

Borneol: Borneol is a monoterpene alcohol found in smaller quantities (around 2–8%) in rosemary oil. A traditional Chinese medicine for its antimicrobial, AIA (anti-inflammatory) & antioxidant activity. Borneol enhances absorption of drugs across the BBB (blood-brain barrier) makes a favorable adjuvant in neurotherapeutics. It also act by disrupting bacterial membranes and inhibiting biofilm formation showing antibacterial property. [9]

Verbenone: Verbenone is a ketonic monoterpene with significant neuroprotective properties. It is especially abundant in specific rosemary chemotypes (e.g., verbenone-type rosemary from Morocco). Verbenone has demonstrated promise in enhancing cognitive performance & may act as an acetylcholinesterase inhibitor, thereby offering benefits in neurodegenerative disorders like Alzheimer's disease. [10] Additionally, it exhibits antioxidant and mild antimicrobial properties, supporting its use in both pharmacological and aromatherapeutic contexts.

The relative concentration of these constituents varies among chemotypes. For instance, rosemary from Tunisia and Spain shows higher levels of 1,8-cineole, while Moroccan rosemary is richer in verbenone. [11]

2. Phenolic compounds

Among the most significant phenolic constituents are carnosol, rosmarinic acid & carnosic acid. These compounds belongs from the class of polyphenols and are found mainly in the leaves and flowering tops of the plant. They exert their effects through various molecular and cellular mechanisms, making rosemary a valuable herb in both phytomedicine and functional food applications. [12]

Carnosic Acid: Carnosic acid is the principal phenolic diterpene in rosemary and may account for up to 4.5% of the plant's dry weight. It is considered a potent natural antioxidant, particularly effective in lipid-rich environments, where it scavenges reactive oxygen species (ROS) and prevents lipid peroxidation. [13] This makes it highly useful in food preservation and nutraceuticals. Pharmacologically, carnosic acid has shown significant neuroprotective effects. It activates the Nrf2/ARE pathway, a critical regulator of cellular antioxidant defense, thereby protecting neurons from oxidative damage. [14] Studies have demonstrated its potential in Alzheimer's disease, where it inhibits β-amyloid aggregation and reduces inflammation in microglial cells. [15] In addition to its neuroprotective activity, carnosic acid also displays anticancer properties. It causes apoptosis and cell cycle arrest in a number of cancer cell lines

including leukemia, breast & colon cancers. It also inhibits angiogenesis and tumor proliferation by modulating pathways of PI3K/Akt/ MAPK/ NF-κB. [16]

Carnosol: Carnosol is a derivative of carnosic acid formed through its oxidation. It shares many of the same bioactivities, including anticancer, antioxidant, AIA (anti-inflammatory) properties. Carnosol inhibits the COX-2 expression & NF-κB activation, both key mediators of inflammation and tumorigenesis. [17] In cancer studies, carnosol has demonstrated activity against prostate, breast, and colon cancer cells by inducing apoptosis, disrupting the cell cycle, and inhibiting metastasis. It also appears to have chemopreventive potential, particularly when combined with other polyphenols. [18] Carnosol has also shown hepatoprotective effects, reducing oxidative stress & liver fibrosis in experimental experiments. Its dual effects (antioxidant /anti-inflammatory) make it promising for treating neurodegenerative disorders & metabolic disorders. [19]

Rosmarinic acid: High amounts of rosmarinic acid, an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid, are present in plants belonging to the Lamiaceae family, including rosemary. It is a hydrophilic polyphenol known for its broad pharmacological spectrum. Rosmarinic acid scavenges free radicals, chelates metal ions, and increases the activity of endogenous antioxidant enzymes such as superoxide dismutase and glutathione peroxidase to produce potent antioxidant effects.[20] It has demonstrated significant anti-inflammatory effects through inhibition of complement system activation, LOX/COX enzymes, TNF-α & IL-6 (pro-inflammatory cytokines) . These actions make it effective in treating allergic conditions, arthritis, and inflammatory bowel disease. [21] Furthermore, rosmarinic acid possesses antiviral activity, having shown efficiency towards viruses that include influenza A, hepatitis B, herpes simplex virus (HSV) potentially through disruption of viral replication and enhancement of host immunity. [22]

3. Flavonoids

Among its various phytochemicals, flavonoids are a significant group contributing to neuroprotective, antioxidant, anticancer activities & AIA (anti-inflammatory). Primary flavonoids identified in rosemary include apigenin, luteolin, and genkwanin. These compounds are known for their diverse biological functions and have attracted attention for their therapeutic potential in chronic diseases, including neurodegeneration and cancer. [23,24]

Apigenin: Apigenin is a flavone found in rosemary in glycosidic and aglycone forms. It is widely recognized for antioxidant, anticancer & AIA (anti-inflammatory) properties. Apigenin show effects by inhibition of COX-2/ iNOS (inducible nitric oxide synthase) and TNF-α and IL-6 down regulation. [25] In cancer research, apigenin has shown promise in suppressing breast enlargement, colon, lung & prostate cells. By promoting arrest of cell cycle, primarily G2 & M phase, induction of apoptosis by modulating p53, Bcl-2, and caspase pathways. [26] Moreover, apigenin has neuroprotective effects through its ability to cross BBB (blood-brain barrier), reduction in oxidative stress, neuronal cells inflammation, makes potential candidate for neurodegenerative disorders like Parkinson's, Alzheimer's. [27]

Luteolin: Luteolin, another important flavone in rosemary, researched for anti-inflammatory, anti-tumor & antioxidant effects. It inhibits pathway signaling of NF-κB, MAPK, STAT3 involved in inflammation & tumor progression. [28] Luteolin can suppress actions of inflammatory mediators, like IL-1β/IL-6/TNF-α, effective in reducing inflammatory responses in conditions such as arthritis and asthma. Luteolin also exhibits potent antioxidant, free radical scavenger & metal chelation. It enhances the body's endogenous antioxidant defense systems by upregulating superoxide dismutase & glutathione peroxidase.[29] Considering anticancer potential, luteolin induces autophagy/ apoptosis in various human cancerous cell lines, inhibits tumor metastasis & angiogenesis. Additionally, it has been demonstrated to make tumor cells more sensitive to chemotherapy to reduce multidrug resistance.[30]

Genkwanin: Genkwanin is a 7-O-methylated flavone found in rosemary and other members of the Lamiaceae family. Though less studied compared to apigenin and luteolin, it shows notable pharmacological activity. Genkwanin possesses anti-inflammatory, cytotoxic, and antioxidant properties. Research indicates that genkwanin can inhibit lipopolysaccharide-induced nitric oxide production and COX-2 expression, suggesting potential anti-inflammatory effects.[31] It has demonstrated cytotoxic effects on leukemia, lung, and colon cancer cells, primarily by inducing mitochondria-mediated apoptosis and cell cycle arrest.[32] Genkwanin also exhibits neuroprotective and antioxidant activities, though its mechanisms are not as well characterized as those of apigenin or luteolin. Its structural similarity to apigenin suggests overlapping biological effects, including ROS scavenging and enzyme inhibition. [33] These compounds are known for their antioxidant, anticarcinogenic, and neuroprotective properties.

4. Triterpenes

Triterpenes are a minor yet pharmacologically significant class of secondary metabolites found in *Rosmarinus officinalis* (rosemary). Among the triterpenes identified in rosemary are ursolic acid and oleanolic acid, both of which exhibit a range of biological activities, including anti-inflammatory, antioxidant, anticancer, and hepatoprotective effects. [34] Ursolic acid is one of the most studied triterpenes in rosemary. It exerts strong anti-inflammatory effects by inhibiting NF-κB activation and downregulating pro-inflammatory mediators like COX-2, IL-1β, and TNF-α. It also promotes apoptosis in cancer cells and inhibits tumor angiogenesis, showing efficacy against various cancers such as colon, breast, and prostate cancers. [35] Oleanolic acid, structurally similar to ursolic acid, possesses hepatoprotective and antioxidant properties. It enhances glutathione production, stabilizes cellular membranes, and protects against oxidative damage in liver cells. [36] Together, these triterpenes contribute significantly to rosemary's therapeutic potential, making it valuable in the development of anti-inflammatory, anticancer, and hepatoprotective agents.

Pharmacological activities of rosemary

Rosmarinus officinalis L. (commonly known as rosemary) is a Mediterranean herb renowned for its culinary and medicinal applications. Its wide range of pharmacological activities is attributed to a rich array of bioactive compounds, particularly phenolic acids (such as

rosmarinic acid), diterpenes (like carnosic acid and carnosol), monoterpenes (including 1,8-cineole and camphor), and various flavonoids. These constituents confer powerful antioxidant, antimicrobial, neuroprotective, and anti-inflammatory properties, which have been validated by numerous preclinical studies.

One of the well-documented effects of rosemary is its antioxidant activity. Compounds such as carnosic acid, carnosol, and rosmarinic acid neutralize reactive oxygen species (ROS) and protect biomolecules from oxidative damage. These antioxidants also enhance endogenous defense systems by upregulating enzymes like superoxide dismutase and glutathione peroxidase, which help in maintaining cellular redox balance. [37] As oxidative stress is a major contributor to aging and chronic diseases—including cancer, neurodegeneration, and cardiovascular disorders—rosemary's antioxidant capacity is of significant therapeutic interest.

Rosemary also exhibits broad-spectrum antimicrobial effects, primarily due to components like 1,8-cineole, camphor, and flavonoids. These compounds disrupt microbial cell membranes, impair metabolic pathways, and inhibit microbial proliferation. Rosemary essential oil has demonstrated activity against both Gram-positive (e.g., *Staphylococcus aureus*) and Gram-negative (e.g., *Escherichia coli*) bacteria, as well as fungal pathogens such as *Candida albicans.* [38,39] These findings support its traditional use in wound healing and food preservation, and its potential as a natural antimicrobial agent.

The neuroprotective properties of rosemary are largely linked to its ability to modulate cholinergic and oxidative stress pathways. Constituents such as rosmarinic acid, carnosic acid, and 1,8-cineole inhibit acetylcholinesterase (AChE), the enzyme responsible for breaking down acetylcholine. This enhances neurotransmission and may improve cognitive function, especially in neurodegenerative diseases like Alzheimer's disease. Furthermore, the antioxidant activity of these compounds helps protect neurons from oxidative damage, reducing the risk of neuronal degeneration. [40]

Rosemary's anti-inflammatory effects are primarily mediated through the suppression of inflammatory signaling pathways. Diterpenes like carnosol and carnosic acid inhibit the activation of nuclear factor-kappa B (NF-κB) and downregulate the expression of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). [41] These actions reduce inflammation in various tissues, suggesting potential benefits in conditions such as arthritis, asthma, and inflammatory bowel disease.

Conclusion:

Salvia rosmarinus (commonly known as rosemary) is a globally significant medicinal and aromatic plant, recognized for its robust phytochemical composition and broad spectrum of therapeutic activities. Originally native to the Mediterranean region, rosemary has been widely cultivated across diverse climates due to its resilience and versatility. Its phytochemical constituents—primarily essential oils, phenolic compounds, flavonoids, and triterpenes—form the foundation of its pharmacological value. Rosemary essential oil, comprising a complex mixture of monoterpenes and diterpenes, is a key contributor to the plant's therapeutic potential.

Major constituents such as 1,8-cineole (eucalyptol), camphor, α-pinene, borneol, and verbenone possess well-documented biological properties. These include anti-inflammatory, antimicrobial, analgesic, and neuroprotective effects. Their synergistic actions enhance the efficacy of rosemary in aromatherapy, phytomedicine, and dermatological formulations. The oil's distinctive camphoraceous aroma and functional benefits have also secured its role in cosmetic and wellness industries. Beyond volatile oils, rosemary is rich in non-volatile phenolic compounds, particularly carnosic acid, carnosol, and rosmarinic acid. These compounds are renowned for their antioxidant capabilities, effectively scavenging reactive oxygen species (ROS) and protecting cellular integrity. They also exhibit anti-inflammatory, anticancer, and neuroprotective activities by modulating various biochemical pathways, including the inhibition of pro-inflammatory enzymes and oxidative stress mediators. This positions rosemary as a promising candidate for the development of natural health products, functional foods, and adjunct therapies in chronic disease management. Rosemary's pharmacological profile is further enhanced by its flavonoid content, notably apigenin, luteolin, and genkwanin. These flavonoids contribute to a wide range of biological actions, such as reducing inflammation, combating oxidative damage, and promoting neuronal health. Their presence complements the activity of other phytochemicals in rosemary, reinforcing its reputation as a multi-functional herb in both traditional and evidence-based medicine. Additionally, the presence of triterpenes such as ursolic acid and oleanolic acid adds to rosemary's therapeutic significance. These compounds have demonstrated hepatoprotective, anti-inflammatory, and anticancer effects in various experimental models. Their inclusion in rosemary's chemical profile broadens the plant's potential applications in pharmaceutical development. Collectively, the diverse pharmacological effects of rosemary are rooted in the interplay of its essential oils, phenolic acids, flavonoids, and triterpenes. These compounds underpin the herb's efficacy as an antioxidant, antimicrobial, neuroprotective, and anti-inflammatory agent. This holistic bioactivity supports its long-standing use in traditional medicine and underscores its growing relevance in contemporary pharmacognosy, nutraceuticals, and cosmeceuticals. While preclinical studies strongly support the therapeutic potential of rosemary, further clinical research is essential to validate its efficacy, safety, and optimal dosing in human populations. Continued investigation into its bioactive constituents and mechanisms of action will pave the way for more widespread and evidence-based use of rosemary in modern healthcare.

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ADAPTOGENIC PROPERTIES OF *WITHANIA SOMNIFERA* (ASHWAGANDHA)

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Abstract:

Withania somnifera, commonly known as Ashwagandha, has emerged as one of the most prominent adaptogenic herbs in conventional and modern medicine. Renowned in Ayurveda for its rejuvenating effects, Ashwagandha has demonstrated promising adaptogenic activity defined as the ability to enhance the body's resistance to physical, emotional, and environmental stressors. This chapter aims to critically evaluate the adaptogenic properties of Ashwagandha by examining its biochemical pathways, molecular mechanisms, and clinical applications. The chapter explores its influence on the hypothalamic-pituitary-adrenal (HPA) axis, cortisol regulation, and neuroendocrine modulation. It also assesses clinical trials that support its use in reducing stress, anxiety, fatigue, and cognitive impairment. Furthermore, the safety, dosage parameters, and potential interactions with pharmaceuticals are discussed. By combining evidence from experimental, preclinical, and human studies, the paper affirms that Ashwagandha holds significant adaptogenic potential, warranting its integration into evidence-based complementary therapy.

Keywords: Ashwagandha, Adaptogen, Stress Response, HPA Axis, Cortisol Regulation

Introduction:

The concept of adaptogens originated in mid-20th century Soviet pharmacology, introduced to describe natural substances that enhance the body's nonspecific resistance to diverse stressors while exerting a stabilizing effect on physiological functions. Unlike conventional stimulants that transiently increase energy or alertness at the expense of disrupting homeostasis, adaptogens has unique provision for the body's capacity to uphold internal equilibrium amid physical, emotional, or environmental challenges without inducing undue physiological strain. [1] This regulatory capacity distinguishes adaptogens as systemic modulators capable of normalizing bodily functions irrespective of whether pathological deviations manifest as excess or deficiency. Fundamentally, adaptogens are characterized by three core criteria: they must be non-toxic and safe when administered at therapeutic doses; they produce a broad-spectrum enhancement of the organism's resistance to stressors including physical, chemical, or biological mediators; and they elicit a balancing or regularizing effect on biological processes regardless of the initial pathological condition. Acting primarily through the neuroendocrine-immune axis, adaptogens mitigate the detrimental consequences of chronic stress, a well-

established contributor to the pathogenesis of numerous disorders such as anxiety, depression, metabolic syndrome, cardiovascular disease, and neurodegenerative conditions.

Within the diverse repertoire of botanical adaptogens, *Withania somnifera*, commonly known as Ashwagandha, has emerged as one of the most extensively studied and clinically validated herbs, renowned for its historical, pharmacological, and therapeutic importance.[2] Indigenous to the arid regions of India, North Africa, and the Middle East, Ashwagandha has been utilized for over three millennia within the Ayurvedic tradition, where it is classified as a Rasayana, a class of rejuvenative herbs reputed to promote longevity, enhance vitality, and bolster resilience against aging and disease.[3] The etymology of "Ashwagandha," which translates to "smell of the horse," alludes both to its distinctive musky aroma and its traditional use in enhancing physical strength, stamina, and sexual vigor. Traditionally, the roots of the plant are predominantly employed, though the leaves, berries, and seeds also contain biologically active constituents. Modern phytochemical research has elucidated a rich profile of bioactive compounds, most notably steroidal lactones known as withanolides, glycosylated derivatives termed sitoindosides, and various alkaloids.[4] These phytoconstituents collectively underpin Ashwagandha's multifaceted pharmacological effects, which include potent anti-inflammatory, antioxidant, neuroprotective, anxiolytic, immunomodulatory, and endocrine-regulating action mechanisms that align strongly with the operational definition of adaptogens.

Despite Ashwagandha's longstanding use in traditional medicine, rigorous scientific investigation into its adaptogenic properties has only accelerated in recent decades with the advent of modern biomedical methodologies. The main purpose of this comprehensive evaluation is to curtly analyze the molecular and systemic mechanisms through which Ashwagandha exerts adaptogenic effects, with particular emphasis on its variation of the hypothalamic-pituitary-adrenal (HPA) axis, regulation of serum cortisol concentrations, and influence on neurotransmitter arrangements including gamma-aminobutyric acid (GABA), serotonin, and dopamine pathways.[5] Furthermore, this study seeks to consolidate evidence from preclinical animal models and clinical trials that assess Ashwagandha's effectiveness in improving stress, anxiety, fatigue, and cognitive impairment. Safety profiles, optimal dosing regimens, and potential herb-drug interactions will also be discussed to evaluate the herb's suitability for integration into contemporary stress management and complementary therapeutic frameworks. By synthesizing insights from phytochemical analyses, molecular pharmacology, and clinical outcomes, this paper endeavors to substantiate whether *Withania somnifera* fulfills the stringent scientific criteria of a true adaptogen and to delineate its potential role as a safe, effective, and evidence-based adjunct in the holistic management of stress-related disorders.

Phytochemistry of *Withania Somnifera*

Withania somnifera (Ashwagandha) is chemically characterized by a complex mixture of secondary metabolites, with steroidal lactones called withanolides and nitrogenous alkaloids being the predominant bioactive classes responsible for its broad pharmacological effects.[6] Withanolides are a distinctive group of C28 ergostane-based steroidal lactones that possess a

highly oxygenated skeleton featuring a lactone or lactol ring typically attached between carbon atoms 22 and 26. These molecules exhibit a variety of structural variations including hydroxylations, epoxidations, and glycosylations, which modulate their biological activities. Among the approximately 40 withanolides identified in Ashwagandha, withaferin A stands out due to its electrophilic unsaturated lactone ring and epoxide group, which facilitate interactions with cellular proteins and transcription factors such as NF-κB, thus mediating potent anti-inflammatory, anticancer, and immunomodulatory effects. Other important withanolides, including withanolide A, withanolide D, and withanone, contribute substantially to Ashwagandha's adaptogenic and neuroprotective capacities by regulating neuroendocrine functions and attenuating oxidative stress. Withanosides, the glycosylated derivatives of withanolides, enhance solubility and bioavailability, further diversifying the herb's therapeutic spectrum.

Complementing withanolides, Ashwagandha's alkaloid profile includes somniferine, tropine, cuscohygrine, anaferine, and anahygrine. These alkaloids, albeit in lower concentrations compared to withanolides, are biologically significant for their neuromodulatory and sedative properties. For instance, somniferine is implicated in promoting restful sleep and calming neural excitability, while tropine's anticholinergic effects modulate parasympathetic nervous system activity.[7] Collectively, these alkaloids act synergistically with withanolides, enhancing the herb's anxiolytic and adaptogenic efficacy. The extraction of Ashwagandha's bioactives is critical to harnessing its therapeutic potential, and it is highly dependent on solvent polarity, temperature, and processing duration. Conventional maceration and percolation techniques using hydroalcoholic solvents (often 70% ethanol) are widely employed to extract a broad spectrum of withanolides and alkaloids due to their ability to dissolve both hydrophilic and lipophilic compounds. However, these methods are time-consuming and can lead to partial degradation of sensitive constituents. Advances in extraction technology have introduced ultrasound-assisted extraction (UAE), which practices ultrasonic waves to disturb plant cell walls and enhance solvent diffusion, significantly improving yield and extraction kinetics. Microwave-assisted extraction (MAE) employs electromagnetic radiation to rapidly heat plant material and solvents, providing an efficient, controlled method for isolating thermolabile withanolides.[8] Supercritical fluid extraction (SFE) utilizing supercritical CO2 modified with co-solvents like ethanol offers a green, solvent-free alternative that selectively extracts nonpolar and moderately polar withanolides with minimal thermal degradation, resulting in highly pure extracts suited for pharmaceutical use.

Standardization of Ashwagandha extracts is paramount to ensuring consistent therapeutic efficacy and safety. Analytical techniques such as high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), and liquid chromatography-mass spectrometry (LC-MS) are employed to quantify total and individual withanolides with high precision.[9] Regulatory guidelines often mandate standardized extracts containing 5–10% total withanolides for clinical applications. Alkaloid content is sometimes quantified to complement

withanolide profiling, though this is less commonly standardized. Chromatographic fingerprinting and chemometric analyses allow comprehensive phytochemical profiling, which aids in authentication, quality control, and detection of adulteration or variability due to geographic or cultivation differences. Furthermore, good manufacturing practices (GMP) ensure standardized extraction procedures, raw material traceability, and batch-to-batch reproducibility, while stability testing guarantees preservation of bioactive content over shelf life. Enhancements in bioavailability have been pursued through formulation strategies such as nanoparticle encapsulation, liposomal delivery, and co-administration with bioenhancers like piperine, which augment systemic absorption and therapeutic outcomes.[10] In summary, the rich and chemically diverse phytochemical profile of *Withania somnifera*, dominated by structurally complex withanolides and bioactive alkaloids, underlies its adaptogenic, neuroprotective, and immunomodulatory effects. The evolution of sophisticated extraction methodologies and rigorous standardization protocols has enabled the development of reproducible, high-quality Ashwagandha products, facilitating their integration into evidence-based herbal therapeutics.

Mechanisms of adaptogenic action of *Withania somnifera*

The adaptogenic properties of *Withania somnifera* (Ashwagandha) are rooted in its multifaceted biochemical and molecular mechanisms that modulate the body's response to various stressors. These mechanisms collectively enhance resilience against physical, emotional, and environmental challenges by restoring homeostasis and protecting cellular function.

Central to Ashwagandha's adaptogenic effect is its capability to regulate the HPA axis, the chief neuroendocrine system governing stress responses. Exposure to stress activates the hypothalamus to release corticotropin-releasing hormone (CRH), which stimulates the pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH then prompts the adrenal glands to produce glucocorticoids, primarily cortisol in humans. Chronic or excessive activation of this axis results in sustained high cortisol levels, which contribute to anxiety, immunosuppression, metabolic disturbances, and neurodegeneration.

Ashwagandha attenuates this overactivation by normalizing CRH, ACTH, and cortisol levels. Experimental studies have shown that administration of Ashwagandha extracts reduces serum corticosterone (the rodent equivalent of cortisol), thereby mitigating the adverse effects of glucocorticoid excess. This normalization is believed to occur through modulation of glucocorticoid receptors and feedback mechanisms that restore HPA axis homeostasis, thus preventing chronic stress-induced damage.[11]

Ashwagandha exerts significant influence on central neurotransmitter systems implicated in stress and mood regulation. One key pathway involves the enhancement of GABAergic signaling. GABA is the chief inhibitory neurotransmitter in the CNS and plays a pivotal role in dropping neuronal excitability and anxiety. Ashwagandha extracts have been demonstrated to increase GABA receptor binding and potentiate GABAergic neurotransmission, thereby producing anxiolytic and calming effects comparable to pharmaceutical agents like benzodiazepines but without the associated dependency risks. In addition, Ashwagandha

modulates serotonergic pathways by increasing brain serotonin levels, which contributes to mood stabilization and antidepressant-like effects. The herb also influences dopamine and noradrenaline systems, which are crucial in attention, motivation, and arousal. By balancing these neurotransmitters, Ashwagandha enhances cognitive function, mood, and resilience to stress. Oxidative stress and inflammation are closely linked to the pathophysiology of chronic stress and neurodegenerative conditions. Stress upsurges the production of reactive oxygen species and pro-inflammatory cytokines, leading to cellular damage and impaired neuronal function.

Ashwagandha exhibits potent antioxidant properties by scavenging free radicals and enhancing endogenous antioxidant defenses such as superoxide dismutase (SOD), catalase, and glutathione peroxidase.[12] These actions reduce oxidative damage to lipids, proteins, and DNA in neural and peripheral tissues. Furthermore, Ashwagandha suppresses the expression of inflammatory mediators like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and nuclear factor-kappa B (NF-κB), thereby reducing neuroinflammation and protecting neuronal integrity. These combined antioxidant and anti-inflammatory effects contribute to the neuroprotective and anti-aging properties of Ashwagandha, making it especially beneficial in conditions exacerbated by oxidative stress. Beyond immediate antioxidant activity, Ashwagandha promotes neuronal survival and regeneration. Studies have demonstrated that withanolides, the bioactive steroidal lactones in Ashwagandha, stimulate neurite outgrowth and synaptic reconstruction, enhancing neural plasticity. This is particularly important in reversing stress-induced hippocampal atrophy and cognitive decline. Ashwagandha also upregulates brain-derived neurotrophic factor (BDNF), a critical neurotrophin involved in neuronal growth, differentiation, and synaptic plasticity. Increased BDNF levels enhance memory, learning, and resilience against neurodegenerative processes. Stress often dysregulates immune responses, leading to either immunosuppression or chronic inflammation. Ashwagandha modulates immune function by balancing pro- and anti-inflammatory pathways. It has immunostimulatory effects that enhance the action of natural killer cells, macrophages, and lymphocytes, thus refining resistance to infections. Simultaneously, it prevents excessive inflammatory responses that can damage tissues.

This bidirectional immunomodulation supports overall homeostasis and contributes to the adaptogenic capacity of Ashwagandha by promoting systemic resilience under stress. Ashwagandha influences various hormonal and metabolic pathways beyond the HPA axis. It has been shown to improve thyroid function by stimulating the synthesis of thyroid hormones (T3 and T4), which adjust metabolism and energy balance. This effect can alleviate fatigue and improve physical endurance. Additionally, Ashwagandha reduces blood glucose levels and improves insulin sensitivity, which can be beneficial under metabolic stress. By stabilizing metabolic parameters, the herb supports sustained energy availability and recovery during prolonged stress.[13]

Preclinical studies

The adaptogenic properties of *Withania somnifera* (Ashwagandha) have been extensively investigated using various established animal models of stress, which simulate human physiological and psychological stress conditions. Common paradigms include chronic restraint stress (CRS), forced swim test (FST), and unpredictable mild stress (UMS). In CRS models, rodents subjected to prolonged immobilization develop heightened corticosterone levels, adrenal hypertrophy, anxiety-like behaviours, and cognitive impairments, all of which are effectively attenuated by Ashwagandha treatment. For example, administration of Ashwagandha in CRS animals normalized corticosterone secretion, reduced adrenal gland enlargement, and improved performance in anxiety-related behavioural assays such as the elevated plus maze and open field tests.[14] Similarly, in the forced swim test, Ashwagandha significantly decreased immobility time, indicating antidepressant-like activity, while in UMS models, it mitigated stress-induced anhedonia and memory deficits. These findings demonstrate Ashwagandha's ability to enhance physiological resilience to diverse stressors. At the biochemical level, Ashwagandha's adaptogenic action is primarily mediated through intonation of the HPA axis, neurotransmitter systems, and oxidative stress pathways. Chronic stress typically induces hyperactivation of the HPA axis, leading to excessive glucocorticoid release, which adversely affects brain regions critical for memory and emotional regulation, such as the hippocampus. Preclinical studies have consistently shown that Ashwagandha suppresses this hypercortisolemia, thereby protecting neural structures from glucocorticoid-induced damage. In parallel, the herb elevates levels of inhibitory neurotransmitters like GABA and serotonin, contributing to its anxiolytic and mood-stabilizing effects, while simultaneously reducing glutamate-mediated excitotoxicity that can exacerbate neuronal injury. Ashwagandha exhibits potent antioxidant and anti-inflammatory properties, foraging reactive oxygen species (ROS), enhancing endogenous antioxidant enzymes, and downregulating inflammatory cytokines such as TNF-α and IL-6. These molecular actions collectively translate into behavioral improvements, including reduced anxiety and depressive-like symptoms, decreased fatigue, and enhanced cognitive function as observed in rodent stress paradigms. Dose-response relationships explored in animal studies further clarify the therapeutic window of Ashwagandha. Moderate doses, often ranging from 200 to 400 mg/kg of standardized root extract, consistently yield the utmost significant biochemical and behavioural benefits without inducing toxicity. Lower doses may produce partial effects, while higher doses above 600 mg/kg generally do not enhance efficacy and may increase the risk of adverse effects, though Ashwagandha is characterized by a wide margin of safety. The adaptogenic activity is primarily attributed to withanolides, the bioactive steroidal lactones, and standardized extracts with defined withanolide content are used in research to ensure consistency and facilitate translation to human clinical dosing.[15]

Clinical evidence

The clinical efficacy of ashwagandha as an adaptogen has been substantiated by numerous randomized controlled trials (RCTs) and observational studies involving diverse populations. Human trials predominantly focus on its capacity to diminish stress and anxiety,

enhance cognitive function, and recover overall quality of life. In several well-designed RCTs, supplementation with standardized Ashwagandha extracts led to important falls in perceived stress scores measured by validated instruments such as the Perceived Stress Scale (PSS) and the Hamilton Anxiety Rating Scale (HAM-A). These reductions were consistently greater than those observed in placebo groups, underscoring Ashwagandha's anxiolytic potential. The mechanistic basis for these effects is thought to lie in Ashwagandha's modulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting to a reduction in circulating cortisol concentrations, which are often elevated in chronic stress and anxiety disorders. Beyond mood regulation, Ashwagandha has demonstrated promising effects on cognitive performance and fatigue management in clinical populations.[16] Studies involving healthy adults experiencing chronic stress, as well as patients with mild cognitive impairment, reveal improvements in memory, attention, and executive functioning following supplementation. Objective neuropsychological tests corroborate subjective reports of enhanced mental clarity and reduced mental fatigue. These cognitive benefits are attributed to Ashwagandha's antioxidant, neuroprotective, and anti-inflammatory properties, which help alleviate the unfavorable effects of stress on brain function. Additionally, Ashwagandha's ability to modulate neurotransmitters such as GABA and serotonin further supports its role in optimizing neural activity and resilience. Clinical trials have also documented improvements in broader quality of life parameters, including emotional wellbeing, sleep quality, and physical vitality. Patients receiving Ashwagandha supplements often report enhanced overall wellbeing and reduced symptoms of stress-related physical exhaustion.[17] These multidimensional benefits highlight Ashwagandha's suitability as a complementary therapy aimed at holistic health promotion. Taken together, the clinical evidence strongly supports Ashwagandha's role as an effective adaptogen that can improve stress-related outcomes and cognitive function while enhancing general quality of life.

Safety, dosage, and interactions

The safety profile of *Withania somnifera* is well-established through both traditional usage and contemporary scientific evaluation. Toxicological studies, including acute and chronic animal models, have demonstrated a high margin of safety for Ashwagandha, with very few adverse effects reported at therapeutic doses. Mild gastrointestinal discomfort, such as nausea or diarrhoea, is the most commonly documented side effect in clinical trials, typically transient and dose-dependent.[18] Importantly, long-term clinical studies have shown that prolonged supplementation, often extending up to several months, is generally well tolerated without evidence of cumulative toxicity or serious adverse events. However, caution is warranted in specific populations such as pregnant or breastfeeding women, where safety data remains limited. Regarding dosage, clinical research has employed a range of standardized Ashwagandha extracts, commonly dosed between 250 to 600 mg per day, often standardized to contain 5–10% withanolides. This dosing regimen aligns with the effective range identified in preclinical dose-response studies and has been consistently associated with improvements in stress, anxiety, cognitive function, and quality of life metrics. The wide therapeutic window and low toxicity risk support the usage of Ashwagandha as a safe secondary or alternative therapy in stress-

related conditions. Potential drug-herb interactions, while relatively uncommon, require attention in clinical practice. Ashwagandha may potentiate the effects of central nervous system depressants, such as benzodiazepines or barbiturates, due to its GABAergic activity, necessitating dose adjustments or monitoring. Additionally, Ashwagandha's immunomodulatory properties may interfere with immunosuppressive therapies, and its potential influence on thyroid hormone levels suggests caution in patients with thyroid disorders or those receiving thyroid medications.[19] Overall, although Ashwagandha is generally safe, healthcare providers should evaluate individual patient factors and concomitant medications to avoid adverse interactions.

Conclusion:

Withania somnifera has emerged as a potent adaptogenic herb with substantial evidence supporting its ability to modulate physiological and psychological responses to stress. Preclinical and clinical studies consistently demonstrate its efficacy in normalizing HPA axis activity, reducing cortisol levels, and improving neurotransmitter balance, which collectively contribute to its anxiolytic, cognitive-enhancing, and fatigue-relieving effects. Compared to other adaptogens, Ashwagandha offers a favorable safety profile and broad therapeutic potential, making it a valuable candidate for integration into evidence-based complementary therapies. While current data are promising, further standardized clinical trials are necessary to optimize dosing, authorize long-term safety, and elucidate molecular mechanisms, thereby facilitating its wider adoption in managing stress-related disorders and enhancing overall wellbeing.

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EXPLORING THE USE OF NATURAL HERBS IN THE MANAGEMENT OF HAEMORRHOIDS

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Abstract:

Hemorrhoids, also known as hemorrhoidal disease, are among the most widespread gastrointestinal conditions globally, with millions affected—particularly older adults. In the United States alone, an estimated 10 million people report symptoms such as anal discomfort, itching, bleeding, and swelling around the anus. Although the condition is common, its underlying causes are not fully understood. However, contributing factors are believed to include genetic predisposition, inadequate fiber intake, irregular bowel habits, and increased intra-abdominal pressure. While both surgical and non-surgical treatments are commonly used, they are often associated with symptom recurrence and undesirable side effects. As a result, there has been a growing shift toward alternative approaches, particularly the use of medicinal plants and dietary therapies. These natural remedies are favored for their affordability, minimal side effects, and deep cultural integration. Traditional systems of medicine, including Ayurveda, Unani, and Traditional Chinese Medicine (TCM), continue to be widely practiced and recognized by the World Health Organization, which notes that plant-based treatments serve as the primary healthcare source for nearly 80% of the global population. A range of medicinal plants—such as *Acacia ferruginea*, *Holarrhena pubescens*, *Mangifera indica*, *Pimpinella anisum*, and *Zingiber officinale*—have shown promise in treating hemorrhoids due to their anti-inflammatory, antioxidant, venotonic, and pain-relieving properties. Studies using animal models, such as croton oil-induced hemorrhoids in rats, have demonstrated the effectiveness of these botanical extracts in alleviating symptoms and combating oxidative stress. Active compounds like flavonoids, terpenoids, and tannins contribute significantly to these beneficial effects by reinforcing vascular health, improving circulation, and reducing inflammation. This review highlights the significant role of herbal medicine in hemorrhoid management and emphasizes the need for further pharmacological and clinical research. Bridging traditional healing practices with modern science may offer more accessible, effective, and safer treatment alternatives, particularly for underserved and rural communities.

Keywords: Hemorrhoids, *Acacia ferruginea*, *Holarrhena pubescens*, *Mangifera indica*, *Pimpinella anisum*, and *Zingiber officinale*

Introduction:

Many people rank hemorrhoids, also known as hemorrhoidal illness, among the most prevalent gastrointestinal disorders. Roughly 10 million Americans reported experiencing hemorrhoids. There is still a lot of mystery around the origin and origin of this illness.[1] This problem can be inherited or caused by factors like the patient's bowel habits being irregular or their diet being poor in fiber. Almost all hemorrhoids presumably originate from bleeding in the lower gastrointestinal tract. Common complaints associated with hemorrhoids include pain or discomfort in the anal area, itching, bleeding, swelling, and the sensation of a mass in the perianal zone. Even while hemorrhoids in children are rare, the fact that they are so common in the elderly is cause for grave worry for generations to come.[2] Patients have experienced a range of side effects, including symptom recurrence, following or during the administration of surgical and non-surgical hemorrhoid treatments. An important part of safe and effective hemorrhoid therapy, in comparison to non-surgical and surgical methods, are nutritional therapies and medicinal plant items.[3] There is evidence that herbal medicines can improve vascular tone, microcirculation in the perivascular amorphous substrate, capillary flow, connective tissue strength, and overall health. Integral to alternative health care systems are traditional medicines and pharmaceuticals derived from herbs. Indigenous practitioners in India employ diverse medicinal plants for the treatment of numerous health conditions. As a key source of health care, traditional medicines derived from plants are relied upon by approximately four-fifths of the world’s population, based on WHO data.[4] A wealth of historically grounded herbal health records can be found in India. Curative and therapeutic herbs have long been an essential aspect of primary health care in western medical systems like Ayurveda and Unani, especially in industrialized countries.[5] Because of its lower risk of side effects, higher degree of cultural tolerance, and superior compliance with the human body, herbal medicine continues to serve as the foundation for essential healthcare system relied upon by 75–80% of people worldwide, especially in impoverished nations. Herbal medicine is significant in rural regions because many people still employ handmade remedies as natural cures for many illnesses.[6] A close bond and mutual respect exist between indigenous people and the natural world. Roughly 4,691 plants have been documented in various medical systems and homeopathic practices for their therapeutic properties, leaving about 2,800 plants either unknown or forgotten to the general public out of the estimated 7,500 plants with proven medicinal properties.[7] Extensive research is underway in the sphere of natural therapies goods to investigate the possibility of medicinal plants as a remedy for hemorrhoids, even if no pharmaceutical has been approved for this purpose as of yet.[8]

Bavasir is a widely used designation for hemorrhoids or bleeding piles. This anorectal condition is rather frequent and affects a large percentage of people. It is characterized by vascular components that extend from the subcutaneous anterior venous plexus in the anal area to the smooth muscle of the anal sphincter through the conjoined longitudinal muscle.[9] Hemorrhoids are found in 4.4% of the general population and 36.9% of those aged 45-65

worldwide.[10] Problems with the anatomy of the anal canal are the root cause of hemorrhoids. In order to facilitate stool evacuation and maintain anal continence, the anal canal is lined with thickened cushions of mucosa and submucosa.[11] Degenerative changes cause a rupture in the cushion's internal connective tissue, which in turn enlarges the vascular plexus and causes hemorrhoidal cushions. These symptoms include perianal epidermal irritation, swelling, prolapse, itching, leaking, and bleeding. Also, hemorrhoids can cause thrombosis, which is both uncomfortable and problematic.[12] Internal hemorrhoids are present inside the anal canal, while external hemorrhoids are beneath the skin surrounding the anus and may bulge either internally or externally. It is possible to improve illness treatment by using or incorporating products with free radical scavenger, wound-healing inhibiting, inflammation-suppressing, pain-alleviating, and skin-softening characteristics.[13]

When external hemorrhoids become thrombosed, they typically cause more obvious symptoms than internal hemorrhoids. When a blood clot forms within the hemorrhoidal vessels, a condition known as thrombosis occurs. This can cause swelling, inflammation, and severe pain. These hemorrhoids can be seen and felt when physically examined because they usually form at the anal orifice or because they extend into the anal cavity.[14] According to embryology, the dentate (pectinate) line, an important anatomical landmark that separates the top two-thirds of the anal canal from the lower third, is located below the anatomical position of external hemorrhoids, which develop from ectodermal tissue.[15]

Anoderm, a specific skin type made of stratified squamous epithelium, covers external hemorrhoids, in contrast to the columnar epithelium that lines and innervates interior hemorrhoids. Somatic sensory nerves, namely inferior rectal nerve branches that originate from the pudendal nerve, provide dense innervation to this area. External hemorrhoids can cause a great deal of pain and suffering, particularly while sitting for long periods, defecating, or exercising, because these somatic nerve fibers supply the very sensitive perianal epidermis. Acute pain and sensitivity commonly seen with thrombosed external hemorrhoids are caused by a mix of vascular congestion and somatic innervation. Hemorrhoids that form close to the rectum are known as internal hemorrhoids. They sit above the dentate line and are endoderm-derived. Due to their vascularization and insulation by visceral nerve fibers and columnar epithelium, they pose no threat.[16] Depth of tissue extension into the anal canal further categorizes internal hemorrhoids as follows: first degree (constantly inside the rectum), second degree (sometimes outside the rectum during bowel movements), third degree (sometimes outside the rectum during bowel movements and needs to be pushed back into the rectum afterwards), and fourth degree (constantly outside the anus).[17]

Underlying causes of haemorrhoids

There has been progress in hemorrhoid treatment, but our understanding of what causes hemorrhoids remains limited. Some of the probable reasons of hemorrhoids Encompass physical habits, restrictive attire, cultural practices, emotional states, climate, inactive lifestyle, and surroundings, susceptibility of the blood vessel wall, inheritance, and inherited propensity. Many

people are at risk, including those with spinal cord injuries, poor bowel habits, chronic constipation or diarrhea, delayed bowel movements, prolonged sitting during defecation, and a low-fiber diet. There are a number of potential causes of elevated intra-abdominal pressure, such as extremely forceful Valsalva defecation, venous blockage during pregnancy, or constipation in the rectal region ampulla. There might be devastating outcomes from cirrhosis brought on by alcoholism or other sources of portal blockage.[18]

Natural plant-derived therapies for haemorrhoids

Herbal and natural remedies for hemorrhoids take a little longer to work but are risk-free compared to conventional treatments and surgeries, which come with a host of additional unwanted side effects like burning, pain, bleeding, itching, and more. Ayurveda is the foundation of Indian longevity medicine that has been around since ancient times. The components of medicinal plants form the basis for the development of several treatments for different diseases. Herbal medicines and ayurveda remedies both stem from plant extracts. Traditional healers, Ayurvedic experts, elders, and indigenous communities possess a treasure trove of information that can be used to create medicinal products. There are fewer adverse effects and more effective results when medicinal herbs are used to treat piles. Everyone has access to natural and herbal therapies. In most cases, the cost is far lower than that of buying conventional pharmaceuticals.[19]

Medicinal plants for treating hemorrhoids

Because it contains potent antioxidants, the hydroalcoholic bark extract of *Acacia ferruginea* had an anti-hemmorrhoidal effect at a dosage of 400 mg/kg in Wistar albino rats that were subjected to a croton-oil-induced model. Docking studies using structure-based pharmacophore mapping were conducted to examine the efficacy of its components, such as oxaprozin, with various target proteins, including prostaglandins, leukotrienes, and interleukins.[20] Examining *Holarrhena antidysenterica's* antioxidant properties, Zahin *et al.* (2009) utilized ferric thiocyanate (FTC), thiobarbituric acid (TBA), and DPPH radical scavenging techniques. While the antioxidant effects of the FTC and TBA techniques were mild, the DPPH radical scavenging activity was extremely low at 20%. An further study conducted by Bhusal *et al.* (2014) examined the antioxidant capabilities of H. pubescens bark. The results showed that both the methanol and ethanol bark extracts revealed substantial DPPH inhibitory effect, with the methanol extract achieving 96% at a concentration of 0.1 mg/mL.

An in-vitro model was used to test a chymotrypsin inhibitor that was derived from an ethanolic seed extract of M. cochinchinensis on hepatic cells. The inducing substance utilized was tert-butyl hydroperoxide. By raising gluthathione levels and decreasing lipid peroxidation levels, it induces cell damage and exhibits significant outcomes.[21] A range of concentrations (6.25, 12.5, 25, 50, and 100 μg/ml) of the methanolic root extract of *P. chinensis* were tested for their antioxidant properties utilizing DPPH, ABTS, SOD, NO radical quenching assay, and reducing capacity assay. The results demonstrate that the scavenging activity increases continuously and is dose-dependent.[22]

Hemorrhoids are known to progress and develop in part because of oxidative stress. Only four of the seventy-one herbs included in traditional healing practices for hemorrhoids—*Acacia ferruginea*, *Bombax ceiba*, *Allium cepa*, and *Holarrhena pubescens*—have had their antioxidant effects studied in both laboratory and animal settings. Traditional medicine systems make reference to the bark of *A. cepa* and *H. pubescens* for gastrointestinal illnesses and piles, and there have been early studies on the effects of the bark's alcoholic and hydroalcoholic extracts. Other antioxidant tests that may add to the anti-hemorrhoid impact can be used to confirm the effectiveness of plant components. The hemorrhoid remedies in traditional Chinese medicine make use of *B. ceiba* flowers, while the bark sample has been used for pharmacological effects. The effectiveness of plant products might be better understood with the use of a comparative research of phytochemicals and pharmacology. A future mechanistic investigation could compare the efficacy of alcoholic and non-alcoholic plant extracts, as well as their bioactive fractions, by studying the levels of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and malondialdehyde (MDA) in anorectal tissue in a patient model of croton oil-induced hemorrhoids. Additionally, researchers can take advantage of the herbs' rich historical use in hemorrhoid treatment in Ayurveda and TCM.

The inflammation lowering properties of an ethanol extract of aerial portions of *Adiantum capillus-veneris* (200 mg) were assessed in mice stimulated with lipopolysaccharide by measuring the spleen index and tumor necrosis factor-related protein expression. The extract has the potential to bring the spleen index and tumor necrosis factor levels back to normal, making it a potential natural anti-inflammatory resource.[23] The tail-flick method and writhing test have also demonstrated antinociceptive effects of *Adiantum capillus*-ethanol venereis extract and ethyl acetate fraction (300 mg/kg orally).[24]

Hemorrhoids can also be treated with *Mangifera indica*. Research on dextran sulfate sodium-persuaded colitis in rats was conducted to evaluate the inflammation lowering properties of *Mangifera indica* water based extract. A dosage of 150 mg/kg of extract was given orally over a two-week period or intravenously for seven days in that research. Later on, myeloperoxidase activity was used to verify that *Mangifera indica* had an anti-inflammatory effect. A decrease in ulceration and myeloperoxidase activity were indicators of the extract's anti-inflammatory properties. Vascular smooth muscle cells and mesenteric resistance arteries of Wistar Kyoto rats were used to assess the vascular effects of *Mangifera indica* extract and mangiferin, a Cglucosylxanthone derivative.38 Using acetic acid-persuaded abdominal constriction and formalin-induced licking, another study demonstrated the analgesic efficacy of an aqueous extract of *Mangifera indica*.[25] An isolated rabbit's aorta ring, with or without endothelium, was used to study the vasorelaxant action of *Rhus coriaria* leaves extract. Endothelium dependence on the vasorelaxant effect was validated by the results.[26]

The inflammation lowering and pain-relieving effects of *Pimpinella anisum* have been demonstrated in animal studies. Analgesic effects of *Pimpinella anisum* essential oil administered orally at a dose of 100 mg/kg were comparable to those of aspirin, according to the

study.[27] Muscle relaxant actions on isolated guinea pig tracheal chains were observed in response to *Pimpinella anisum* essential oil, water based and ethanol extracts, and inhibitory activities on muscarinic receptors. This may have a calming influence on the veins.[28]

In vivo research on *Terminalia chebula's* wound-healing capabilities revealed strong effects on the healing process. Male albino rats had their skin wounds treated topically with an alcoholic extract (200 µL) from the plant's leaves. A decrease in epithelization, an improvement in the pace of contraction, and faster wound healing were also seen.[29] The same was done with *T. chebula*, however this time the researchers used the plant's immature fruits to extract tannins. Sprague-Dawley rats were given a topical application of 5 mg of tannin extract for each cutaneous wound after being stabbed. According to the findings of the study, the treatment groups exhibited meaningfully increased levels of vascular endothelial growth factor expression, collagen organization, wound contraction, and granulation formation compared to the control groups.[30]

The inflammation lowering properties of *aloe vera* have been recognized for a long time. A rat study looked at the effects of *aloe vera* extracts in three different forms: water, chloroform, and ethanol, on paw edema caused by carrageenan. The swelling could be reduced by using the chloroform and water-based extracts. Experimental evidence has also shown that *aloe vera* gel has anti-inflammatory effects on inflammatory bowel illness.[31]

Experimental research have revealed that *Zingiber officinale* possesses inflammation lowering and analgesic properties. *Zingiber officinale* ethanol extract (50-800 mg/kg intraperitoneally) showed substantial, dose-dependent pain-relieving and inflammation lowering effects in comparison to morphine (10 mg/kg) and diclofenac (100 mg/kg) in acetic acid and hot-plate tests, as well as in fresh egg albumin-persuaded pedal edema.[32] In acetic acid-persuaded writhing and formalin-persuaded testing, 6-gingerol (25-50 mg/kg), one of the primary ingredients, showed pain-alleviating and inflammation-reducing effects.[33]

Animal studies with carrageenan-induced inflammatory pain, plantar, hot plate, pin prick, and mechanical allodynia tests (400 mg/kg) demonstrated the analgesic and anti-inflammatory properties of *Citrus medica* peel extract.[34] An anti-inflammatory drug might be provided using the ruta graveolens methanol extract, which inhibited edema effectively in an arthritis rat model (20 mg/kg for 21 days).[35] Traditional and folk remedies for hemorrhoids from different countries have been investigated in earlier studies.[36] Some of the symptoms that these medicinal plants have been known to alleviate include rectal prolapse, heavy periods, bleeding, and pain. Those enhancements were achieved by venotonic, laxative, pain-alleviating, inflammation-reducing, and venoprotective mechanisms. With respect to the therapeutic plants used in the Middle Ages, this study examined their pain-alleviating, inflammation-reducing, venotonic, and vasorelaxant activities. Previous research has demonstrated that 64 of the 105 medicinal plants have analgesic or anti-inflammatory properties. The majority of investigations were conducted as animal research, with only two publications pertaining to human subjects. Flavonoids, tannins, and terpenoids are examples of active secondary metabolites that contribute to the traits listed

above. It is clear that flavonoids, one family of medicinal chemicals, have been utilized to treat hemorrhoids. These chemicals appear to slow the worsening of symptoms, as well as inflammation, discomfort, and bleeding.[37]

Conclusion:

The purpose of this research was to investigate the probable processes that may be responsible for the therapeutic benefits of a variety of herbs that have historically been used for the treatment of hemorrhoids in a methodical and thorough manner. According to the findings of a comprehensive investigation into the medicinal herbs that have been reported, more than half of them exhibit noteworthy anti-inflammatory and analgesic characteristics. These properties are believed to contribute significantly to the effectiveness of these herbs in reducing hemorrhoidal symptoms on a major level. There is a growing corpus of experimental and preclinical research that highlights promising pharmacological actions, despite the fact that there is a conspicuous scarcity of clinical trials in human populations that evaluate the efficacy and safety of these herbal treatments. These discoveries provide scientific backing for the historical and traditional applications of such plants, indicating that they have the potential to serve as valuable leads for the creation of novel pharmacological drugs. Consequently, the combination of traditional knowledge with contemporary scientific methodologies has the potential to lead the way for the identification of therapeutic choices that are both successful and safer for the management of hemorrhoids.

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HERBAL REMEDIES FOR INSOMNIA: A NATURAL PATH TO RESTFUL SLEEP

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Abstract:

Insomnia is a prevalent sleep condition marked by challenges in beginning or sustaining sleep, resulting in considerable daytime dysfunction. It stems from a multifaceted interaction of psychological, physiological, and behavioural elements, accompanied by neurobiological disturbances involving critical neurotransmitters including GABA and serotonin. Traditional pharmaceutical interventions offer symptomatic alleviation but are frequently constrained by adverse effects, tolerance, and dependency concerns. This chapter examines the pathophysiology, etiology, and contemporary pharmacological treatment of insomnia, highlighting the increasing interest in herbal therapies as safer, natural alternatives. Numerous medicinal herbs possessing sedative and anxiolytic effects have demonstrated potential in enhancing sleep quality by influencing neurochemical pathways associated with sleep regulation. Notwithstanding encouraging first findings, additional clinical investigations are vital to confirm their effectiveness and safety. Combining herbal methods with conventional treatments may provide a comprehensive and successful approach to controlling insomnia and improving overall sleep quality.

Keywords: Insomnia, GABA and Serotonin, Sedative, Anxiolytic Effects

Introduction:

Humans allocate one-third of their lifespan to sleep. A sufficient quantity of quality sleep is essential for individuals to sustain effective daytime functioning and psychological well-being. Approximately 10% to 30% of the population experiences a sleep disturbance.[1] insomnia is among the most prevalent type of sleep disturbance, defined by difficulty in initiating or sustaining sleep effectively.[2] Subpar sleep quality leads to adverse effects on daytime activities, evident in mood fluctuations, fatigue, and memory lapses. Insomnia is the second most prevalent ailment reported following pain. The prevalence of sleeplessness was shown to be even greater among the elderly population.[3] Reports indicate that 20% to 40% of the elderly experience sleep disturbances, with 25% of this population suffering from insomnia. It also found that women are more prevalent than men.[4]

Insomnia markedly diminishes general well-being, leading to chronic weariness, diminished focus, emotional volatility, and an increased susceptibility to mental health issues, including anxiety and depression.[5] The cognitive and psychological repercussions not only

impair daily functioning but also diminish quality of life and elevate the risk of chronic disease. Traditional therapies such as benzodiazepines and non-benzodiazepine hypnotics, while useful in the short term, frequently entail negative consequences like diurnal somnolence, cognitive deterioration, dependence, and withdrawal manifestations, particularly with extended usage.[6] Consequently, there is an increasing worldwide fascination in herbal and natural therapies for insomnia. Medicinal plants including Valeriana officinalis (valerian), Matricaria chamomilla (chamomile), and Passiflora incarnata (passionflower) have become increasingly popular due to their sedative properties and positive safety ratings.[7] These natural alternatives are progressively adopted for their capacity to address sleep disorders with minimal adverse effects, along with a holistic and integrative health approach.[8]

Types of insomnia

Insomnia is categorized into three primary kinds according to length and frequency: transitory, acute, and chronic. Transient insomnia endures for many nights, typically under a week, and is frequently induced by temporary stressors such as travel, environmental alterations, or emotional turmoil. Acute insomnia, or short-term insomnia, lasts for a duration of up to three weeks and is generally linked to prolonged stress, sickness, or lifestyle disturbances.[9] Transient and acute insomnia can go away independently if the underlying reasons are addressed. Chronic insomnia can be identified when sleep disruptions manifest at least three evenings weekly and endure for a minimum of three months. It is frequently complex, encompassing psychological, physiological, and behavioural elements.[10] Chronic insomnia may persist long after the initial trigger is addressed, frequently necessitating a multifaceted care strategy that includes cognitive behavioural therapy, modifications to lifestyles, and even pharmaceutical intervention.[11]

Causes of insomnia

Insomnia may stem from various underlying reasons, which can be broadly classified into psychological, physiological, and lifestyle-related issues. Psychological variables are prevalent triggers, with stress, worry, and sadness significantly contributing.[12] Individuals suffering from emotional discomfort or racing thoughts frequently encounter challenges in initiating or maintaining sleep, and these symptoms are closely associated with interrupted sleep patterns.[13] Chronic stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increased cortisol levels that disrupt the regular sleep-wake cycle. Some physiological explanations include illnesses like persistent discomfort, asthma, GERD, and hormonal imbalances like menopause or thyroid problems. Any of these health issues can make it difficult, if not impossible, to get a good night's sleep. People may find it challenging to stay in the deeper, restorative stages of sleep if they are experiencing pain or inflammation, for instance, since these conditions can heighten nightly arousals.[14]

Insomnia can also be brought on by certain aspects of one's daily routine. Stimulants, such as caffeine or nicotine, taken just before bed might postpone the start of sleep. When people don't follow a normal sleep pattern, use electronics in the hours leading up to bed, or do intellectually taxing activities in the middle of the night, it throws off their body's natural

melatonin production and circadian rhythm.[15] Blue light from screens inhibits the body's natural production of melatonin, making it even more difficult to fall or stay asleep. The importance of behavioural therapies targeting these modifiable elements in treating insomnia is being more acknowledged.[16]

Pathophysiology

The etiology of insomnia is complex, encompassing several dysfunctions in neurological, related to hormones, and behavioural mechanisms that regulate the sleep-wake cycle. A key notion in comprehending insomnia is heightened alertness, denoting elevated degrees of arousal in cognitive, emotional, and physiologic aspects.[17] Functional neuroimaging studies indicate that individuals with insomnia display heightened metabolic activity in wake-promoting brain regions (including the thalamus, brainstem, and anterior cingulate cortex) even during sleep, implying an inability to downregulate arousal systems at night. This elevated level of vigilance is additionally corroborated by augmented high-frequency EEG activity (beta and gamma waves) during non-REM sleep, indicating brain hyperactivation.[18]

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis at the neuroendocrine level is pivotal in the etiology of insomnia. Chronic insomniacs consistently exhibit elevated cortisol levels, particularly throughout the evening and early night, which disrupts circadian rhythms and impedes sleep onset.[19] Furthermore, autonomic imbalance, marked by heightened sympathetic nervous system activity and diminished parasympathetic tone, exacerbates cardiovascular and metabolic hyperactivation during sleep, as indicated by elevated overnight heart rate and blood pressure in individuals with insomnia.[20]

Neurotransmitter-level anomalies in gamma-aminobutyric acid (GABA) signaling are associated with insomnia. GABA serves as the principal inhibitory neurotransmitter in the brain and is crucial for the initiation and sustenance of sleep. Decreased GABA levels have been observed in the brains of individuals with insomnia, especially in the occipital cortex, indicating compromised inhibitory regulation of arousal pathways.[21] Furthermore, heightened activity in orexin (hypocretin) neurons, which facilitate awake, has been hypothesized to further disrupt sleep-wake regulation; however, additional study is required in this domain.[22]

A further aspect of insomnia pathogenesis pertains to cognitive-emotional imbalance. Individuals with insomnia frequently demonstrate chronic concern for sleep, resulting in performance anxiety at night and a continuous cycle of dissatisfaction and hyperarousal that sustains their sleeplessness.[23] This is seen by heightened activation in the amygdala and prefrontal cortex, areas linked to emotional processing and executive function, even during rest or efforts at sleep. Over time, insomnia gets conditioned, transforming the bed and bedroom, formerly linked to rest, into stimuli for alertness and anxiety—a phenomena elucidated by classical conditioning models.[24] Insomnia is not solely a nocturnal issue but a 24-hour condition characterized by the dysregulation of processes that promote sleep and arousal at various levels. This comprehension has transformed therapy paradigms to focus on both physiological arousal and maladaptive cognitive-behavioural patterns in persistent insomnia.

Pharmacological management of insomnia

The contemporary pharmacological treatment of insomnia predominantly involves benzodiazepine receptor agonists (bzras), including conventional benzodiazepines (e.g., temazepam, lorazepam) and novel non-benzodiazepines, sometimes referred to as "Z-drugs" (e.g., zolpidem, zaleplon, eszopiclone). These drugs target GABA-A receptors, augmenting inhibitory neurotransmission to facilitate sleep induction. Benzodiazepines, although helpful for short-term treatment, pose concerns of tolerance, dependence, next-day sedation, and cognitive impairment, especially in older persons.[25] Z-drugs are frequently favored due to their abbreviated half-life and diminished residual effects; however, prolonged usage may result in negative consequences, including intricate sleep disorders such somnambulism or sleep driving.[26] Moreover, novel drugs like orexin receptor antagonists (e.g., suvorexant and lemborexant) have surfaced as intriguing options, specifically targeting the wake-promoting orexin neuropeptides. These medications have shown effectiveness in enhancing sleep initiation and preservation with a more advantageous safety profile; nevertheless, cost and accessibility may restrict their utilization.[27]

Concurrently, non-pharmacological interventions are increasingly prioritized as primary or supplementary approaches, especially for persistent insomnia. Cognitive Behavioural Therapy for Insomnia (CBT-I) is the gold standard, addressing dysfunctional sleep tenets behavioural patterns, and hyperarousal.[28] Cognitive Behavioural Therapy for Insomnia (CBT-I) encompasses methods such as stimulus control, sleep restriction, relaxation training, and cognitive restructuring, demonstrating long-term efficacy comparable to pharmacological treatments without the associated hazards.[29] Furthermore, sleep hygiene education, bright light treatment, and mindfulness-based stress reduction (MBSR) are being investigated as supplementary methods to mitigate circadian disturbances and diminish arousal. These therapies are particularly advised for elderly patients or those with comorbidities, as sedative drugs may provide considerable dangers.[30]

Herbal approaches for managing insomnia

Herbal medicine has garnered significant interest as a natural substitute for traditional pharmacotherapy for insomnia, providing anxiolytic and sedative advantages with typically reduced side effects and decreased risks of reliance. Traditional medicinal systems such as Ayurveda, Traditional Chinese Medicine, and Western Herbalism have historically employed specific plants to address sleep-related disorders. Numerous herbs exhibit mechanisms related to GABA modulation, anxiolytic effects, and circadian rhythm regulation, rendering them suitable options for mild to moderate insomnia.

Valerian root (*Valeriana officinalis*)

Valeriana officinalis, or valerian, is among the most thoroughly researched and routinely utilized herbal treatments for insomnia. The calming properties of valerian are mainly due to its interaction with the GABAergic system in the central nervous system. Substances including valerenic acid, valepotriates, and lignans have been identified as inhibitors of GABA

degradation, a crucial inhibitory neurotransmitter that facilitates relaxation and sleep.[31] Numerous clinical investigations have established valerian's effectiveness in enhancing sleep latency, sleep quality, and subjective sleep pleasure, especially in those experiencing mild to moderate insomnia. A meta-analysis conducted by Fernandez-San-Martin *et al.* revealed small advantages of valerian extract relative to placebo, with no notable side effects. It is generally prescribed in doses between 300 and 600 mg, consumed 30 minutes to two hours prior to sleep. The herb is often safe and well-tolerated; nevertheless, some users have reported moderate adverse effects, including dizziness or stomach distress.[32]

Hops (*Humulus lupulus*)

Humulus lupulus (hops) is renowned for its sedative and hypnotic properties and has been conventionally employed to address sleep disorders and moderate insomnia. The active compounds, including humulone, lupulone, and xanthohumol, are thought to engage with the GABAergic system, augmenting inhibitory neurotransmission and facilitating sedation. Research indicates that hops extract, particularly when combined with valerian, can diminish sleep latency and enhance sleep quality in persons suffering from insomnia. Clinical research indicates that hops may have modest hypnotic effects by influencing circadian rhythms and augmenting melatonin activity. Notwithstanding encouraging results, further comprehensive, large-scale studies are required to definitively ascertain its efficacy and safety profile in the treatment of insomnia.[34]

Kava-kava (Piper methysticum)

Kava-kava a traditional plant from the South Pacific, is recognized for its anxiolytic and calming effects, positioning it as a viable herbal treatment for insomnia, especially when associated with anxiety. Kavalactones, the active chemicals, alter GABA-A receptors, diminish excitatory neurotransmission, and facilitate relaxation without substantially compromising cognitive performance.[35] Clinical research has indicated enhancements in sleep quality, shortened sleep latency, and a reduction in nocturnal awakenings among persons suffering from stress-induced insomnia. Nonetheless, apprehensions over hepatotoxicity have restricted its extensive therapeutic application, leading to demands for standardized extracts and better dosage protocols. Kava continues to be a viable option for the short-term treatment of sleep disturbances linked to anxiety.[36]

Chamomile (Matricaria recutita)

Chamomile is a commonly utilized medicinal herb recognized for its soothing sedative and anxiolytic effects, rendering it beneficial in the treatment of mild to moderate insomnia. The therapeutic efficacy is primarily ascribed to apigenin, a flavonoid that interacts with benzodiazepine receptors in the brain, facilitating relaxation and sleep without the adverse effects linked to synthetic hypnotics.[37] Clinical and preclinical research have shown that chamomile extracts can enhance sleep latency and quality, especially in individuals experiencing sleep problems related to worry or stress. It is deemed safe for all age demographics and is

frequently provided as tea or pills. Nevertheless, more rigorous, large-scale trials are required to validate its long-term efficacy and dosing protocols.[38]

St. John's Wort *(Hypericum perforatum)*

St. John's Wort is chiefly recognized for its antidepressant properties, although it has also demonstrated potential in enhancing sleep, especially in cases of insomnia linked to mild to moderate depression. The active components—hypericin, hyperforin, and flavonoids—regulate neurotransmitters like serotonin, dopamine, and norepinephrine, which are intricately associated with mood and sleep control.[39] Certain research indicate that Hypericum perforatum may aid in normalizing interrupted sleep patterns by augmenting melatonin secretion and reinstating circadian regularity. Although it may not function as a direct sedative, its capacity to alleviate anxiety and depressed symptoms can indirectly enhance sleep quality. Nonetheless, it may interact with several drugs, including SSRIs and oral contraceptives, requiring caution in its administration.[40]

Passionflower *(Passiflora incarnata)*

Passionflower is a conventional herbal therapy recognized for its anxiolytic and mild sedative properties, rendering it effective in the treatment of insignificant insomnia, particularly when associated with stress or restlessness. The therapeutic impact is thought to result from the modulation of the GABAergic system, enhancing GABA levels in the brain, which promotes relaxation and diminishes neuronal excitability.[41] Clinical studies indicate enhancements in sleep latency, duration, and quality, especially with the short-term consumption of passionflower tea or extract. It is typically well-tolerated with negligible side effects, rendering it appropriate for a wide array of individuals. Nevertheless, additional standardized trials are required to ascertain appropriate dosage and long-term efficacy.[42]

Skullcap *(Scutellaria lateriflora)*

Skullcap, a traditional North American plant, is recognized for its mild sedative and anxiolytic effects, perhaps enhancing sleep in persons with insomnia associated with nervous tension or anxiety. The bioactive chemicals, chiefly flavonoids like baicalin and wogonin, are believed to engage with the GABAergic system, augmenting inhibitory neurotransmission and facilitating relaxation.[43] Despite its prevalent usage in folk medicine and over-the-counter sleep aids, clinical research on skullcap is few, with the majority of evidence being from in vitro and animal studies indicating central nervous system depressive effects. Initial data suggest it may effectively decrease sleep latency and enhance sleep maintenance; nevertheless, further rigorous human trials are necessary to confirm its safety and effectiveness characteristics.[44]

Vervain *(Verbena officinalis)*

Vervain is conventionally utilized as a soothing herb with gentle sedative effects, rendering it a possible natural treatment for insomnia and anxiety-induced sleep disruptions. The calming effects are ascribed to several bioactive substances, including iridoid glycosides and flavonoids, which may regulate the central nervous system by affecting neurotransmitter routes including GABA and serotonin. While scientific investigations on vervain's impact on insomnia

are scarce, certain preclinical studies indicate its potential to alleviate nerve tension and enhance relaxation, hence corroborating its traditional application for enhancing sleep quality. Additional clinical trials are required to confirm its efficacy and establish suitable dose for sleep disorders.[45]

Herbal methods for addressing insomnia offer intriguing alternatives to traditional treatments by focusing on the neurochemical pathways involved in sleep regulation, including the GABAergic and serotonergic systems. These natural therapies frequently provide soothing and anxiolytic benefits with less risk of adverse effects and reliance relative to conventional pharmacological alternatives. Despite preliminary studies indicating beneficial benefits on sleep quality and reduced sleep latency, further rigorous clinical research is necessary to ascertain their efficacy, appropriate doses, and safety profiles. Integrating herbal therapies can be an essential aspect of a comprehensive approach to facilitate restorative sleep, particularly for those pursuing milder and more natural remedies.

Conclusion:

In a nutshell insomnia is a complicated and widespread sleep disease with numerous origins, including psychological stress, anxiety, physiological abnormalities, and lifestyle factors. The pathogenesis entails complex neurochemical disturbances, especially in the modulation of neurotransmitters like GABA, serotonin, and melatonin, which are essential for sustaining appropriate sleep patterns. Traditional pharmacological interventions, such as benzodiazepines, non-benzodiazepine hypnotics, and other sedative compounds, have shown effective in enhancing sleep; nevertheless, they frequently entail disadvantages including tolerance, reliance, and negative side effects. Their limitations have generated heightened interest in complementary and alternative medicines, particularly herbal remedies that provide a more natural method for sleep regulation.

Herbal medications had a rich historical background in traditional systems and are increasingly acknowledged for their sedative, anxiolytic, and sleep-enhancing effects, which are facilitated by diverse neurochemical mechanisms. The evidence for numerous herbal therapies is substantiated by both preclinical and clinical investigations, however the quality and scope of this research differ. Herbal medicines generally exhibit less side effects and reduced dangers of dependency, rendering them appealing alternatives for persons pursuing safer long-term solutions for insomnia. However, the standardization of herbal extracts, optimization of dosages, and thorough clinical evaluations are essential domains for future research to guarantee efficacy and safety.

Ultimately, the integration of herbal methodologies with conventional therapy within a holistic framework can facilitate individualized and effective management of insomnia. This method targets both symptoms and underlying causes, lifestyle variables, and patient preferences. This comprehensive approach shows potential for promoting sleep quality, improving overall well-being, and alleviating the impact of insomnia on individuals and healthcare systems.

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ROLE OF HERBAL ANTIOXIDANTS IN ATHEROSCLEROSIS PREVENTION

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Abstract:

The main causes of atherosclerosis, one of the primary causes of cardiovascular disease, are inflammation, lipid peroxidation, and oxidative stress. Herbal antioxidants, including terpenoids (curcumin, ginkgolides), polyphenols (quercetin, resveratrol), and organosulfur compounds (allicin), provide benefits for health by scavenging reactive oxygen species (ROS), suppressing inflammatory pathways like NF-κB, enhancing endogenous antioxidant enzymes (SOD, CAT, GPx), and inhibiting LDL oxidation. Studies both preclinical and clinical demonstrate the ability of substances like resveratrol and curcumin to enhance endothelial function and lessen the development of plaque. Advances such as nanoparticle and liposomal formulations offer promise, despite being constrained by bioavailability and standardization difficulties. The therapeutic value, sources of information, and mode of action of herbal antioxidants in reducing the risk of atherosclerosis are examined in this chapter.

Keywords: Atherosclerosis, Herbal, Antioxidants, Reactive Oxygen Species, Prevention

Introduction:

Atherosclerosis, a serious inflammatory condition, is the primary contributory factor of coronary heart disease and strokes in humans.[1] It is characterized by intimal plaques and the accumulation of cholesterol in arterial walls.[2] The Greek term for atherosclerosis consists of two parts: atherosis (fat buildup with macrophages) and sclerosis (fibrotic layer containing smooth muscle cells, connective tissue, and leukocytes).[3]

Major cardiovascular illnesses (CVDs), including coronary artery disease, peripheral arterial disease, and stroke, are caused by this condition and together contribute significantly to worldwide morbidity and mortality". Important risk factors that have been connected to the development of atherosclerosis include high levels of C-reactive protein (CRP), stress, alcohol consumption, smoking, immunological disorders, vascular wall inflammation, genetic predispositions, bacterial infections, insulin resistance, hypertension, type 2 diabetes, obesity, hypercholesterolaemia, and dyslipidaemia.[4] It is brought on by a complex interaction of endothelial dysfunction, oxidative stress, inflammation, and fat accumulation.[5] The development of atherosclerosis-related cardiovascular disease is significantly influenced by oxidative stress. Excessive production of oxygen species that are reactive (ROS) and oxidized low-density lipoprotein (Ox-LDL) are its defining characteristics. Excess ROS can cause endothelial damage, oxidation of low-density lipoprotein (LDL) particles, and the stimulation of

pro-inflammatory pathways, all of which are factors in the formation and instability of plaque. The primary cause of oxidative stress is an imbalance between the creation of radicals (the synthesis of reactive oxygen and/or nitrogen species) and the antioxidant defense system's radical scavenging mechanisms.[6]

CVDs also place significant financial and social strains on the healthcare system because of employee absenteeism, lengthy rehabilitation, and high hospital and medication expenses. As a result, the world's top public health priorities are to prevent smoking, obesity, diabetes mellitus, and CVDs. Cardiovascular illnesses can be prevented by quitting smoking, maintaining a healthy weight, exercising, and adopting healthy eating habits. Despite their effectiveness, traditional pharmaceutical treatments including beta-blockers, statins, and antiplatelet medicines may have drawbacks, such as side effects and insufficient protection.[7] Alternative or complementary therapies are being investigated because, despite their effectiveness, traditional pharmacological approaches may have drawbacks and adverse consequences. Even when traditional pharmaceutical interventions are helpful, they may have drawbacks and adverse consequences, which is why alternative or complementary medicines are being investigated. Consequently, complementary and alternative methods are becoming more and more popular, especially those that use natural antioxidants found in dietary plants and herbs.[8]

Herbal antioxidants

Herbal antioxidants have garnered increasing attention in recent years as possible treatments and preventative measures for atherosclerosis. Rich in polyphenols, flavonoids, terpenoids, and alkaloids, herbal antioxidants have been shown to scavenge free radicals, prevent LDL oxidation, and regulate inflammatory reactions. For example, several studies have demonstrated the prospective anti-atherogenic qualities of substances like quercetin from onions, resveratrol from grapes, and curcumin from Curcuma longa. In addition to having antioxidant properties, these organic substances also affect endothelial function, lipid metabolism, and atherogenesis-related gene expression. [9,10]

Scavenging free radicals

Oxidative stress causes a considerable increase in ROS, which are remnants of metabolism of cells that include hydrogen peroxide, superoxide anions, and hydroxyl radicals. ROS, such as hydrogen peroxide (H2O2), singlet oxygen, hydroxyl radicals and superoxide anion, are commonly produced by biological reactions occurring inside cellular systems or by external factors.[11] Excessive ROS can lead to elevated amounts of lipid peroxides and free radicals, which are the pathophysiology of degenerative diseases like atherosclerosis, if they are not eliminated by the antioxidant framework.[12] ROS are "neutralized" by antioxidants before they may react with biological components and change their structure or function. Flavonoids and related phenolic compounds are examples of plant-derived antioxidant agents that have a variety of natural effects, including antioxidant activity in cells. By giving electrons, herbal antioxidants—particularly polyphenols—can neutralize these free radicals and stop the lipid peroxidation chain events that lead to atherosclerosis.[13]

Inhibiting LDL Oxidation and Enhancing Endogenous Antioxidant Enzymes

In comparison to synthetic medications, herbal supplements are becoming more and more popular because they are less expensive, easier to use, and have fewer adverse effects. LDL oxidative modification is intimately associated with atherosclerosis, a primary cause of cardiovascular diseases (CVDs) that leads to the production of plaque in arteries. Finding natural antioxidants that stop LDL oxidation is essential to the fight against CVDs. One traditional medicinal herb that has shown significant antioxidant activity is *Butea superba*. Despite its well-known advantages for enhancing sexual health and rejuvenation, new research shows that it can also scavenge free radicals and prevent LDL oxidation. The main way that *Butea superba* prevents atherosclerosis is by preventing the oxidation of LDL, which is a crucial step in the creation of plaque. The plant, which is abundant in flavonoids and phenolic compounds, prevents the oxidative alteration of LDL particles by neutralizing the reactive species of nitrogen and oxygen (ROS and RNS). This lessens the buildup of plaque and foam cells in artery walls. Furthermore, *B. superba* may contribute to cardiovascular protection by reducing oxidative stress, preserving endothelial function, and lowering vascular inflammation. Moreover, herbal antioxidants help the body's natural antioxidant mechanisms. Antioxidant enzymes including glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) have been demonstrated to be activated more by compounds like silymarin and curcumin, which helps lower lipid peroxidation and intracellular oxidative stress. [14-16]

Classification of herbal antioxidants

Herbal antioxidants are plant-based bioactive substances that are essential for scavenging free radicals and avoiding oxidative stress and related illnesses. Their functional characteristics and chemical structures allow for a comprehensive classification (Table 1).

Table 1: Botanical antioxidant classification

Class	Subclasses with examples	Primary Sources	Health benefits	Reference
Polyphenols	Flavonoids (e.g., quercetin), Phenolic acids (e.g., caffeic acid), Stilbenes (e.g., resveratrol), Lignans (e.g., secoisolariciresinol), Tannins	Fruits, vegetables, tea, wine, seeds	Antioxidant, anti-inflammatory, cardioprotective	[17,18]
Terpenoids	Monoterpenoids (e.g., limonene), Sesquiterpenoids (e.g., curcuminoids), Diterpenoids (e.g., ginkgolides), Triterpenoids (e.g., ginsenosides), Tetraterpenoids (e.g., carotenoids)	Essential oils, herbs, spices, fruits	Antioxidant, anti-inflammatory, Neuroprotective	[19]

Organosulfur Compounds	Allicin, S-allyl cysteine	Garlic, onions	Antioxidant, cardioprotective, antimicrobial	[20]
Alkaloids	Berberine, Caffeine, Morphine	Berberis, coffee, opium poppy	Antioxidant, neuroprotective, anti-inflammatory	[20]
Tannins	Hydrolyzable (e.g., gallotannins), Condensed (e.g., proanthocyanidins)	Tea, wine, berries	Antioxidant, antimicrobial, anti-inflammatory	[18]
Lignans	Secoisolariciresinol, Matairesinol	Flaxseeds, sesame seeds	Antioxidant, estrogenic, cardioprotective	[17]

Herbal antioxidants in atherosclerosis prevention

Curcumin

Turmeric's (*Curcuma longa*) main bioactive ingredient, curcumin, has strong anti-inflammatory and antioxidant qualities that help preserve against atherosclerosis. The suppression of LDL oxidation is one of the main ways curcumin provides its anti-atherosclerotic benefits. An important factor in the development and advancement of atherosclerotic plaques is oxidized LDL. Research has indicated that curcumin can lessen LDL's susceptibility to oxidation, which in turn lessens the production of oxidized LDL and the development of plaque. [21]

Curcumin also affects the gene expression of genes related to lipid uptake and storage, which in turn modifies lipid metabolism. Curcumin, for example, has been demonstrated to suppress the expression of CD36 and fatty acid-binding proteins, which are linked to foam cell production and lipid accumulation in macrophages. Curcumin also improves the body's defence against oxidative stress by enhancing the activity of endogenous antioxidant enzymes, like glutathione peroxidase (GPx), and CAT. Curcumin's anti-inflammatory capabilities are crucial in the context of atherosclerosis. Curcumin inhibits NF-κB, a transcription factor that regulates the generation of pro-inflammatory cytokines and adhesion molecules. Curcumin suppresses NF-κB activation, reducing inflammation in the blood vessel endothelium and preventing plaque growth and endothelial dysfunction. [22]

Resveratrol

A polyphenol phytoalexin, resveratrol is found in many plant species, such as *Arachis hypogaea* (peanuts), *Morus rubra* (mulberries), *Vitis vinifera* (grapes), *Veratrum grandiflorum* (white hellebore), *Polygonum cuspidatum* (Japanese knotweed) and the compound, a resorcinol byproduct from a Veratrum species, is known by its source, hence the term "resveratrol." There are numerous targets for resveratrol, which is the chemical foundation underlying its many

pharmacological activities. Some specific molecules of resveratrol are directly physically interacting with it, whereas others are indirectly regulated (e.g., by changes in expression levels). More than 20 compounds that directly bind to resveratrol have been found. Resveratrol promotes eNOS activity in a variety of mechanisms, including upregulating eNOS expression, increasing eNOS activity as an enzyme, and inhibiting eNOS uncoupling. Resveratrol improves endothelial function and reduces arterial stiffness by increasing NO bioavailability, both of which are critical for decreasing the risk of atherosclerosis. [23]

Quercetin

A flavonoid that is widely found in many fruits and vegetables, including berries, apples, and onions, quercetin has been thoroughly researched for its potential cardiovascular advantages, especially in preventing atherosclerosis. Quercetin, a natural drug, inhibits inflammatory molecules like VEGF, MCP-1, IL-6, and IL-1β, resulting in significant anti-inflammatory effects.[24] Quercetin inhibits the endoplasmic reticulum stress chop pathway, which reduces the production of atherosclerosis.[25] and activating the production of the paraoxonase 1 gene, NFK-β factor, and caspase-3.[26] Macrophages' secretion of inflammatory substances can likewise be inhibited by quercetin. Zhang *et al.* (2016) discovered that in a rat model of cerebral ischaemia caused by IL-1β and IL-6, quercetin reduces the severity by reducing the inflammatory factor IL-1.[27] According to Si *et al.* (2016) quercetin inhibits the formation of prostaglandin E2 (PGD2), COX-2, and NO by modulating the NF-κB and MAPK signalling pathways. Additionally, in animal models, quercetin was shown to stabilize atherosclerotic plaque by suppressing the ERK signaling pathway, which in turn decreased the expression of matrix metallopeptidase (MMP)-1 and MMP-9.[28]

Garlic

Allium sativum, or garlic, has been shown to provide therapeutic benefits, especially for cardiovascular health. Its therapeutic actions against atherosclerosis are facilitated by its bioactive components, particularly allicin. Garlic's ability to decrease cholesterol is one of its main advantages. Garlic's capacity to reduce the fatty substance in arterial walls has been related to its preventive effect against atherosclerosis. At the arterial wall level, garlic has significant antiatherogenic (preventive) and antiatherosclerotic (inducing regression) actions.[29] Malic enzyme, glucose-6 phosphate dehydrogenase , 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase, and fatty acid synthase were among the lipogenic and cholesterogenic enzymes whose hepatic activity were inhibited by garlic.[30] Following garlic feeding, there was a rise in the excretion of acidic and neutral steroids, which garlic was also shown to improve cholesterol excretion.[31] Human participants' LDL extracted after receiving age plus aqueous garlic extract was found to be much more resistant to oxidation. [32]

These findings suggest that one of the potent mechanisms behind garlic's protective effects against atherosclerosis may be inhibited LDL oxidation.[33] Initially, it was established that allicin was the active component responsible for the antiatherosclerotic activity. Recent in vitro research, however, has shown that water-soluble organosulfur compounds—particularly S-

allyl cysteine (SAC), found in garlic oil and diallyl-di-sulfide (DADS), found in old garlic extract—are also strong inhibitors of cholesterol formation. [34][35]

Green tea catechins

Epigallocatechin gallate (EGCG) is the most prevalent and bioactive of the several catechins found in green tea (*Camellia sinensis*). The cardiovascular preventive benefits of EGCG, particularly with regard to the prevention of atherosclerosis, have been thoroughly investigated. Antioxidant Properties: By eliminating ROS, EGCG demonstrates strong antioxidant activity. This lowers oxidative stress and stops LDL particles from oxidizing, which is a crucial stage in atherogenesis.[36] This antioxidant impact slows the development of atherosclerotic lesions and preserves endothelial function. In addition to its antioxidant qualities, EGCG has strong anti-inflammatory effects. It inhibits the transcription factor NF-κB, which regulates gene expression adhesion molecules and pro-inflammatory cytokines, from becoming activated. EGCG lowers endothelial dysfunction and vascular inflammation via inhibiting NF-κB activation, two factors that are essential for the formation of atherosclerotic lesions. By altering the processes involved in the absorption and production of cholesterol, EGCG also affects lipid metabolism. Research has demonstrated that EGCG can increase HDL cholesterol while decreasing total and LDL cholesterol, resulting in a better lipid profile and a lower risk of atherosclerosis.[37]

Ginkgolides

One of the oldest surviving tree species, ginkgo biloba, has been utilised in traditional medicine for ages. Ginkgolides and bilobalide, two of its main ingredients, have garnered scientific interest due to their varied pharmacological characteristics, especially their function in preventing atherosclerosis and protecting the cardiovascular system. The most common ginkgolides are terpene lactones called ginkgolide A, B, and C. They are distinguished by their special capacity to suppress platelet-activating factor (PAF), a potent phospholipid mediator involved in inflammation, vascular thrombosis, along with platelet aggregation. The probability of thrombus development, a serious consequence of atherosclerosis that can result in myocardial infarction or stroke, is decreased by ginkgolides' inhibition of PAF, which also decreases platelet adhesion and creation.[38]

In addition to their antithrombotic properties, ginkgolides contain powerful antioxidants that remove ROS and protect the vascular endothelium from oxidative harm. This is important because LDL oxidation and oxidative stress are important atherogenesis initiators. It has been demonstrated that ginkgo extracts increase the production of NO, which enhances endothelial function and encourages vasodilation. This reduces peripheral resistance and promotes healthy blood flow, both of which are critical in reducing cardiovascular risk.[39]

The table summarizes the mechanisms through which various herbal antioxidants contribute to atheroprotection (Table 2).

Table 2: Mechanisms of herbal antioxidants in atheroprotection

Herbal antioxidant	Source	Mechanisms in atherosclerosis prevention	References
Curcumin	*Curcuma longa* (Turmeric)	Inhibits LDL oxidation, Regulates lipid metabolism (↓ CD36, FABPs), Enhances antioxidant enzymes (GPx, CAT, SOD), Suppresses NF-κB → ↓ inflammation and plaque formation	[20,21]
Resveratrol	Grapes, Mulberries, Peanuts, Japanese Knotweed	Enhances eNOS activity and NO production, Improves endothelial function, Reduces arterial stiffness	[23]
Quercetin	Berries, Apples, Onions	Anti-inflammatory (↓ VEGF, MCP-1, IL-6, IL-1β), Inhibits ER stress and apoptotic pathways, Regulates NF-κB and MAPK signaling, Stabilizes plaques via ↓ MMP-1 and MMP-9	[24-28]
Garlic	*Allium sativum*	Inhibits cholesterol synthesis enzymes (e.g., HMG-CoA reductase), Promotes cholesterol excretion, Inhibits LDL oxidation (via allicin, DADS, SAC), Antiatherogenic and antiatherosclerotic effects	[29-35]
Green Tea Catechins (EGCG)	*Camellia sinensis*	Antioxidant: ↓ ROS and LDL oxidation, Anti-inflammatory: inhibits NF-κB, Modulates lipid profile (↓ LDL, ↑ HDL), Preserves endothelial function	[36,37]
Ginkgolides	*Ginkgo biloba*	Inhibits platelet-activating factor (PAF) → ↓ thrombosis, Antioxidant: scavenges ROS, Enhances NO production → vasodilation and improved endothelial function	[38,[39]

Conclusion:

The leading causes of atherosclerosis include endothelial dysfunction, oxidative stress and inflammation which is still a serious public health concern worldwide. Because they alter

these fundamental processes, herbal antioxidants provide a comprehensive preventative strategy. Certain phytochemicals, such as ginkgolides, curcumin, resveratrol, and quercetin, have demonstrated promise in lowering oxidative damage, enhancing vascular function, improving lipid metabolism, and reducing inflammation. Their methods, which include the activation of endogenous antioxidant defenses, ROS scavenging, and prevention of LDL oxidation, highlight their therapeutic value. Clinical translation is still constrained by issues with bioavailability, formulation uniformity, and an extended safety profile, despite promising results from in vitro, animal, and early human research. Standardized extracts, thorough clinical trials, and advancements in drug delivery technologies are necessary to confirm the safety and effectiveness of these treatments for broad therapeutic usage. By combining traditional cardiovascular treatments with herbal antioxidants, an integrated approach may have a synergistic effect and lessen the impact of atherosclerosis along with its repercussions. Further investigation into the pharmacokinetics, molecular mechanisms, and clinical results of herbal antioxidants may unlock the door to their optimal use in the therapy and prevention of cardiovascular disease.

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