APTI women's forum

APTI Women's Forum Newsletter

Phytopharmaceuticals: Immense potential for India

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Editor's Note

Prof. Vandana B. Patravale
The Chief Editor,
APTI Women's Forum Newsletter

Dear Readers,

In 2015, Drugs and Cosmetics Act and Rules 1945 was amended to create a new category of drugs called phytopharmaceuticals. Indian Pharmacopoeia 2022 has launched seven phytopharmaceutical ingredients (PPI) monographs and three in 2024 addendum. A significant portion of the worldwide population relies upon herbal treatment and so it is essential to regulate the phytopharmaceutical products. Keeping this in mind, the theme for September – December, 2024 APTI women's newsletter is **"Phytopharmaceuticals: Immense potential for India"**.

The newsletter provides comprehensive information on herbal innovations, several Indian phytopharmaceutical ingredients, their formulation, market analysis, regulatory framework, and their application in various diseases. There are articles that compare the traditional knowledge with modern advancement in phytopharmaceutical growth. Some articles explore the therapeutic potential of Indian plants like *Ginkgo biloba, Andrographis paniculata, Lantana camara,* etc. whereas some articles explore the Indian plants that can be utilized as nutraceuticals, boosting immunity, and for treatment and/or management of cancer, gastric ulcer, cardiovascular disorder, and polycystic ovarian syndrome.

The editorial board is certain that you will get equal interest from reading this issue focused on geriatric healthcare as you did from reading our prior APTI Women Forum Newsletters. We express our utmost gratitude to all the authors for their diligent work in making this newsletter very enlightening. I express my gratitude to the whole editorial team for their tireless efforts, which included both the conceptualization and editing of the reviews provided by authors from different parts of the country. I would like to convey my thanks and gratitude to Prof. Vanaja K, Dr. Shubhini Saraf, Dr. Jubie Selvaraj, Dr. Rakhi Khabiya, Dr. Rashmi Trivedi, Prof. Preeti Suresh, Dr. Madhavi Bhavaraju, Ms. Niyamat Chimthanawala, Dr Vaishali Shirsat for providing editorial comments to the articles. Also, thanks to Dr. Clara Fernandes for providing puzzles for the newsletter.

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Propagation of novel phytoformulation approaches: The path ahead

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Abstract

During early history, human beings used natural resources, along with animals, plants, and minerals, as primary sources of therapeutic substances. Traditional remedies, also known as phytopharmaceuticals, are a fundamental aspect of phytomedicine. The World Health Organization reports that in most underdeveloped nations, 70%–95% of individuals predominantly depend on traditional medicine for treatment. Herbal medicinal treatments, known as phytopharmaceuticals, are pharmaceutical formulations derived from plant ingredients. For centuries, various cultures have utilized herbal medicinal treatments, also known as phytopharmaceuticals, to address wide range of health conditions. These treatments leverage the therapeutic benefits of diverse plant parts, including leaves, roots, stems, flowers, and fruits, to create remedies in various forms such as teas, tinctures, extracts & powders. This is due to the therapeutic effects of the active compounds present in these plants, various nanocarriers are used in pharmaceutical sciences and discussed in this review various approaches of nanocarriers of Indian medicine.

Keywords: Phytopharmaceuticals, Herbal Plants, Indian Medicine, Nanoparticles, Phytosomes, Ethosomes.

1. Introduction

Plants contain many metabolites in the hundreds of thousands. Metabolites are chemicals formed and involved in metabolic processes that serve several activities, including signalling, enzyme inhibition, defence, enzyme cofactor roles, and plant protection against different infections and illnesses. Researchers have identified diverse plant species and genera that synthesize both primary and secondary metabolites of various sorts. Advancements in metabolism have facilitated the profiling of many metabolites. Metabolomics involves the thorough investigation of diverse metabolites inside a biological system. Furthermore, it enhances understanding of the organisation and principles of cellular functions at many levels, providing knowledge into physiological processes within an integrated system (1,2).

The terms "phytopharmaceutical" and "phytopharmakon" derive from Greek terminology. "Phyto" is derived from "phyton," signifying "plant," while "pharmakon" denotes "medicine." A phytomedicine is characterised as unadulterated standardised extract from a medicinal plant or its components,

containing at least four bioactive or plant-based compounds that are qualitatively and quantitatively evaluated. The drug is intended for either internal or externally application in humans or animals for the detection, therapy, alleviation, or prevention of diseases or disorders, except via parenteral route (3,4).

2. India's herbal legacy

Medicinal herbs are being utilised a significant resource for the treatment of numerous ailments since antiquity. Traditional medical systems, such as Unani practitioners (Hakims) and Indian healers (Vaids), have utilised medicinal herbs for more than 4,000 years. Historical records demonstrate the extensive utilisation of herbs in European and Mediterranean societies for medicinal purposes (5). Ayurveda, Siddha, Unani, and Homeopathy are traditional treatment methods cited in ancient Indian texts, such as the ancient literature. Approximately 8,000 herbal medicines are accessible under the AYUSH systems can be found in India. Vedas, originating from 5000–1000 BC, are regarded as the oldest Indian literature and provide comprehensive knowledge of natural medicines. Furthermore, we consider the "Charaka Samhita," which concentrates on internal medicine, and the "Sushruta Samhita," which highlights surgery, as foundational books of Ayurveda (6). Traditional folk medicine has historically utilised extracts from several plants and their components, as recorded in the Wealth of India compendium, to address numerous ailments. India's diverse biodiversity serves as a substantial reservoir of medicinal plants, enhancing its enormous herbal resource base for therapeutic applications (7). In the recent decades, the utilisation of plant based medications has gained popularity because of constraints of contemporary therapies in managing chronic diseases and the considerable adverse consequences linked to them. Bioactive chemicals originally extracted from plants have facilitated the creation of numerous contemporary medications and their synthetic variants. *Mucuna pruriens* (L-Dopa), *Taxus brevifolia* (paclitaxel), *Rauvolfia serpentina* (reserpine), and *Catharanthus roseus* (vincristine and vinblastine) represent prominent examples. These phytochemicals have significantly contributed to the progression of contemporary pharmacological development (8).

Numerous studies exist regarding the therapeutic potential of plant isolates. Standardised extracts from *Commiphora guggul* and *Zingiber officinale* serve as notable citations within the phytoformulations category of medicine that are commonly given by doctors (9,10).

The Indian Government in the year 2013 promulgated a new rule for 'Phytopharmaceutical pharmaceuticals' as in addition to the pharmaceuticals and Cosmetic Rules of 1945, delineating the regulatory criteria for these substances. This official declaration delineates the definition and regulatory stipulations for phytopharmaceutical pharmaceuticals. Submission criteria must encompass scientific facts related to quality and safety. Assessment of effectiveness to permit marketing of a herbal medication under similar conditions. In connection to synthesized chemical molecules, Appendix 1B in Schedule Y of the Drugs and Cosmetics Act of 1940 and the Rules of 1945 delineates the regulations for conducting clinical studies or engaging in the importation/manufacturing of phytopharmaceuticals. Drugs in the country include critical information, pharmacognostic data, the processing of extracts/phytopharmaceuticals, and formulation. Data on stability, safety, toxicity, and human or clinical pharmacology (11). Our country, renowned for its rich heritage of herbal medicine, has taken a leading role in the global regulatory framework by establishing guidelines for the regulation of phytopharmaceutical drugs. This initiative ensures the standardization, safety, and efficacy of plant-based medicines, promoting their integration into modern healthcare systems both nationally and internationally (6).

In India, some 25,000 phytotherapeutic compounds are utilised in conventional and folk medicine (12). The quantity of plant varieties employed in different system are as under : Ayurveda, Siddha, Unani, Homoeopathy shown in figure 1 (13). Over 7,500 species of plants are presently utilised in Indian Medicine comprising tonics, antimalarials, antipyretics, aphrodisiacs, expectorants, hepatoprotectants, antirheumatics, and diuretics (14, 15), in addition to the treatment of specific central neurological disorders (16-18).

Indian Herbal Medicines (IHMs) are gathered from the entire plant or specific organs, including

branches, leaves, tree bark, roots, blossoming flowers, and seeds, in addition to animal and mineral sources. Some medications are sourced from the excretory secretions of plants, such as gum. Herbal formulations known as Rasayans are employed for resurgence and the mitigation of the ageing process, hence promoting long-term sustainability (19, 20).

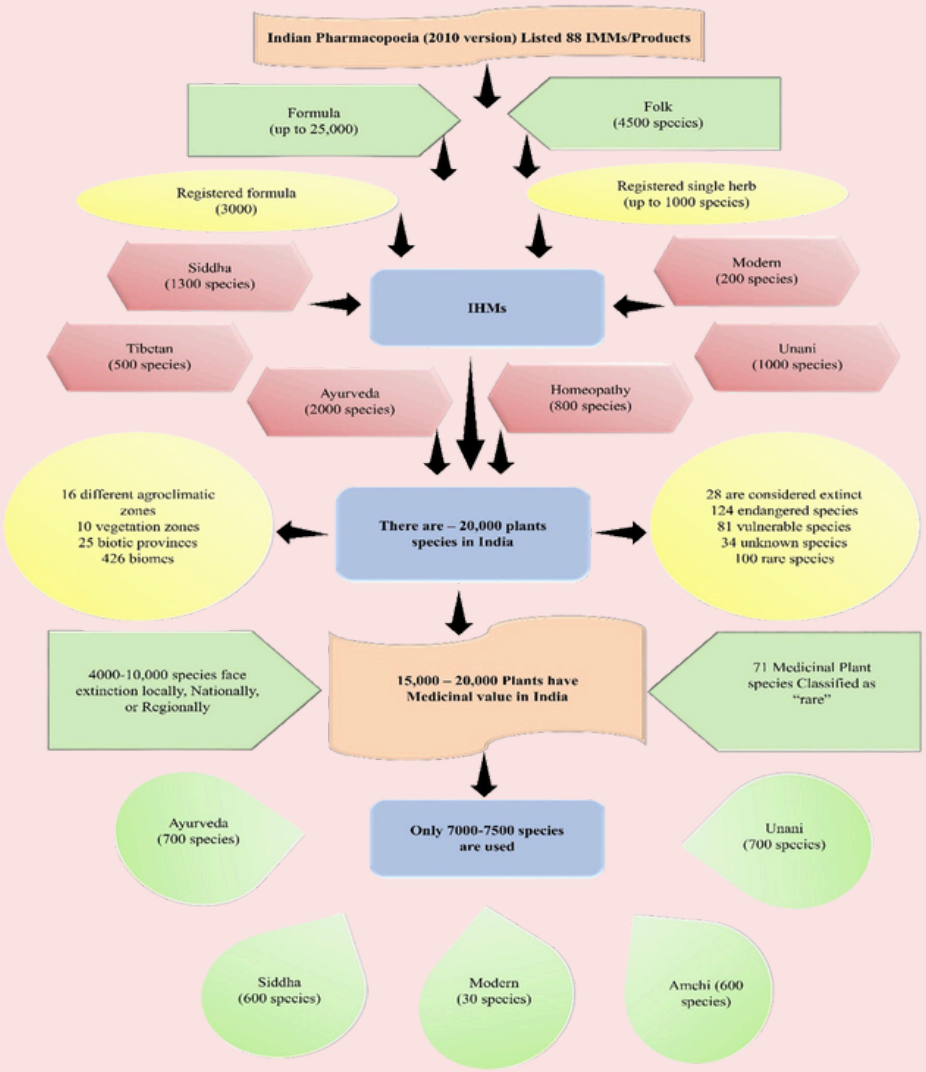

Figure 1. Various Indian plant species and Indian Herbal Medicines (IHMs)

3. Recent advancements in the herbal drug delivery approach

Over the last twenty years, nanotechnology has been utilized for efficient drug delivery and targeted pharmaceutical applications in specific tissues (21). Enhanced pharmaceutical delivery methods facilitate reducing detrimental effects and attaining improved efficacy, which is advantageous for the patients. Some important features of herbal therapies may include: better solubility of components, higher bioavailability, higher absorbency, lower herbal dosages, achieving steady-state therapeutic drug levels, and overall better compliance (22). Researchers use different ways to deliver drugs to get around physical problems like the blood-brain barrier (BBB) or to find long-lasting ways to give drugs besides oral delivery, which could damage the chemicals (21). Allopathic medications currently primarily use Novel Drug Delivery Systems (NDDS). Recent focus has shifted towards utilising NDDS for the safe, effective, and proven formulation of 'ayurvedic' herbal drugs, which may present a compelling option in the current context. Here is the list of some novel drug delivery approaches discussed in Table 1.

S. No.	Developed Phyto-formulation	Preparation Method	References
01.	Phytosomes (Quercetin, Oxymatrine, Ginkgo biloba, Marsupium, Embelin, Naringenin, Silybin)	**Solvent ether-injection process:** This process involves the interaction of lipids solubilised in an organic solvent with botanical extracts in a water layer. Phospholipids solubilized in diethyl ether is added dropwise into aqueous phase having phyto-ingredients which are be entrapped. It causes the production of cellular vesicles, which then lead to the formation of complexes when the solvent is removed. The structure of phytosomes is determined by their concentration; amphiphiles in the mono state are created while the concentration is low, but a range of structures with varied forms, such as round, cylindrical, disc, and cubic or hexagonal vesicles, can be formed as the concentration increases.	(23-29)
02.	Nanoparticles (Berberine, Quercetin, Hypocrellins, Silybin, Ginseng, Salvia miltiorrhiza, Pacltaxe-loaded)	a) Emulsion solvent evaporation method b) The two nanoparticle compositions (berberine/heparin and berberine/heparin/chitosan) were prepared using a simple ionic gelation process and magnetic stirring at ambient temperature	(30-35)
03.	Microspheres(Ginsenoside,Quercetin, Zedoary oil, Rutin)	Fresh leaves from *Ficus benghalensis* (Banyan), *Syzigium cumini* (Jamun), and *Ocimum sanctum*(Tulsi) were harvested. To create PHC-based microspheres, a non-aqueous solvent evaporation approach was used with minor changes to previous literature methods. PHC and all of the materials (polymers) were combined with acetone in varied proportions, added to liquid paraffin, and mechanically stirred for 8 hours at 1500 rpm. After evaporating the solvent, the microspheres were filtered, washed using n-hexane a number of times to remove any remaining oil, and dried at room temperature. Finally, they were kept in sterile containers.	(36-39)
04.	Ethosomes (*Sophora alopecuroides*, Matrine)	Ethosomal formulations made up of 2-5% Phospholipon 90 (PL), 20-50% ethanol, the medication or probe as stated, and 100% water by weight were prepared. Phospholipon and a pharmaceutical agent or a fluorescence probe were solubilised in ethanol. Double distilled water was incrementally introduced in a fine stream, with continuous agitation at 700 rpm utilising a Heidolph digital 2000, RZR-2000, within a specially designed sealed container for this procedure. The mixing process was extended for an additional 5 minutes. The system was maintained at 30°C during the preparation phase and subsequently permitted to cool to ambient temperature.	(40, 41)

05.	Liposomes(Magnolol, *Nux vomica,* Quercetin, Diospyrin, *Myrtus communis, Artemisia arborescens,* Puerarin)	Multilamellar vesicles (MLVs) were produced by the thin film hydration process. A particular quantity of surfactant, cholesterol, and arborescens essential oil (12.5 mg/ml) was dispersed in 10ml of chloroform in a 50 ml flask. The solvent was removed by vaporization under decreased pressure at ambient temperature. The lipid film was hydrated with distilled water at 60°C via mechanical stirring. The condenser was attached to a chloroform-containing cold trap. Then, for 60 minutes, spin the ultracentrifuge (Beckman L80M) at 4^{o}C and 30,000 RPM. The supernatant was collected and the oil content was determined by measuring the absorbance at 284 nm with a Hitachi-U 2000 UV/VIS spectrophotometer.	(42-48)
06.	Solid Lipid Nanoparticle (Curcumin, Curcuminoids)	A concentrated dispersion of curcumin SLNs were made using oil in water micro-emulsification process.	(49-51)
07.	Emulsion(*Azadirachta indica*, Matrine, Berberine,Rhubarb, Docetaxel, Quercetin, Silybin)	Microemulsion- solution A was made by combining all of the necessary materials in an adequate volumetric flask. For solution B di-n-butyl tartrate, 1-butanol, SDS, and sodium tetraborate aqueous buffer of 10 mM at pH 9.2 were dissolved. The two solutions were subjected to sonication for 30 min. until transparent microemulsion was formed. ACN in various quantities was added to microemulsion solution B.	(52-56)

4. Conclusion

Research initiatives in developing countries, like India, are actively studying indigenous medicinal plants. This necessitates extensive research on phytopharmaceuticals to optimize drug screening from diverse biological sources. The scientific examination of nutraceuticals and pharmaceuticals, specifically plants used for nutrition and regularly consumed as a preventive strategy against disease, is a pertinent area of inquiry. Phytoconstituents, such as flavonoids, tannins, and aldehydes, exhibit well-documented activities, including antioxidant properties and free radical scavenging. These compounds are important in chronic inflammation management, including cancer, diabetes, and wound healing. Numerous research opportunities exist for the scientific evaluation of plant-based remedies, which may offer safer, more cost-effective, and less toxic alternatives for self-medication compared to current prescription medications.

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The rise of phytopharmaceuticals in India: Opportunities and innovations


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Abstract

Phytopharmaceuticals are pharmaceutical products that contain active ingredients derived from plants or parts of plants (e.g., leaves, roots, flowers, and seeds). They represent a category of medicinal products that stand between herbal medicines and chemically synthesized drugs. Phytopharmaceuticals undergo rigorous scientific evaluation, including clinical trials, and are required to meet the same standards of efficacy, safety, and quality as conventional pharmaceutical products. The history of phytopharmaceuticals in India is deeply rooted in the country's traditional medicinal systems, which have utilized plant-based remedies for thousands of years. India has a rich heritage of using plants for medicinal purposes, most notably through Ayurveda, Siddha, Unani, and Tibetan medicine. Over time, the traditional knowledge of herbal medicines has evolved into modern phytopharmaceuticals, where scientific validation, standardization, and regulatory oversight have become integral parts of drug development.

Keywords: Biodiversity, Standardization, Traditional medicine

1.Introduction

Phytopharmaceuticals, hold significant potential for India due to its rich biodiversity and long history of traditional medicine like Ayurveda, Unani, and Siddha. With the global shift toward natural and plant-based treatments, India is well-positioned to capitalize on this trend for various reasons including Rich Biodiversity and Traditional Medicine Systems. India is one of the world's most biodiverse countries, home to over 45,000 plant species, many of which have medicinal properties. This gives India a natural advantage in sourcing raw materials for phytopharmaceuticals. India's traditional medicine systems like Ayurveda and Unani already use plant-based ingredients. These systems offer a vast pool of knowledge that can be integrated into modern phytopharmaceutical research, creating products with both historical credibility and modern efficacy. These differ from Ayurvedic, Siddha or Unani (ASU) therapies, because phytopharmaceuticals, as defined under the Drugs and Cosmetics Act, 1940, must include a purified and standardized fraction with a defined minimum of four bio-active or phytochemical compounds of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation or prevention of any disease or disorder. These ASU therapies fall under the Ministry of AYUSH, whereas phytopharmaceuticals are regulated by the Central Drugs Standards Control Organization (CDSCO) (1).

2. Historical milestones in phytopharmaceutical development in India

2.1. Ancient and traditional medicine (3000 BCE onwards)

- **Ayurveda:** The roots of phytopharmaceuticals in India go back to the ancient Vedic texts (like the Rig Veda) and classical Ayurvedic texts such as the Charaka Samhita (circa 1000 BCE) and Sushruta Samhita (circa 600 BCE). Ayurveda emphasized the use of medicinal plants, minerals, and metals for treating various ailments (2).
- **Medicinal plants:** Common plants used in ancient Ayurvedic remedies include Ashwagandha (*Withania somnifera*), Neem (*Azadirachta indica)*, Tulsi (*Ocimum sanctum*), Turmeric (*Curcuma longa*), Amla (*Phyllanthus emblica)*, and Brahmi (*Bacopa monnieri*).
- **Polyherbal formulations:** Ayurveda often used combinations of plant extracts in polyherbal formulations like Triphala, Chyawanprash, and Dashmool, which are still used today for their therapeutic properties.
- **Siddha and Unani:** Both the Siddha (prevalent in Tamil Nadu) and Unani (introduced by Persian and Arab influences) systems of medicine in India also heavily relied on the medicinal properties of plants. Many of these plants are now being investigated for their potential in modern phytopharmaceuticals.

2.2. Colonial period (17th to 20th Century)

- During the British colonial period, India's traditional knowledge of herbal medicine began to be documented systematically. British botanists and scientists established herbariums, botanical gardens, and research institutes to catalog India's vast biodiversity of medicinal plants (3).
- British and European scientists also started researching and extracting active compounds from Indian medicinal plants. For example, quinine was isolated from Cinchona bark (used for treating malaria), and ephedrine was extracted from the plant Ephedra, long used in Indian and Chinese traditional medicine.

2.3. Post-independence era (1947–1980s)

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- After India's independence in 1947, there was a renewed focus on the development of traditional medicine and herbal drugs. Research institutions like the Central Council for Research in Ayurvedic Sciences (CCRAS) and the Central Drug Research Institute (CDRI) were established to scientifically study and validate the efficacy of traditional herbal formulations (4).
- The Council of Scientific and Industrial Research (CSIR) played a significant role in the standardization, extraction, and study of bioactive compounds from medicinal plants. For example, ashwagandha, neem, brahmi, and tulsi were researched extensively during this period for their pharmacological potential.
- Indian pharmaceutical companies such as Dabur, Himalaya, Zandu, and Charak Pharma began focusing on modernizing and marketing traditional herbal medicines, which eventually became phytopharmaceuticals.

2.4. Modern era (1990s–Present)

- **Phytopharmaceuticals as a recognized category:** In the late 20th and early 21st centuries, India began to align with international standards of drug development, including the phytopharmaceutical sector. The Government of India formally recognized phytopharmaceuticals as a distinct category under the Drugs and Cosmetics Act, 1940 in the 2015 Amendment (5).
- Phytopharmaceuticals are defined as plant-derived medicines with standardized bioactive compounds, undergoing rigorous clinical trials and quality control, much like allopathic drugs.
- **Ayurvedic and herbal drug market:** Indian companies started developing patented formulations derived from traditional knowledge but validated through modern scientific methods. For example:

    - **Himalaya's Liv.52** (a liver tonic) and **Dabur's Chyawanprash** are examples of traditional formulations that have undergone modern scientific validation.

- **Phytopharmaceutical Innovations**: In recent years, newer phytopharmaceuticals like BGR-34 (an antidiabetic drug derived from plant sources, developed by CSIR) have been launched, showcasing the merging of traditional knowledge with modern pharmacology.
- **Research and Development:** Indian institutes like the National Botanical Research Institute (NBRI), Indian Council of Medical Research (ICMR), and various pharmaceutical universities have been collaborating with the pharmaceutical industry to develop, standardize, and test phytopharmaceuticals through clinical trials. Indian pharmaceutical companies and research institutions are increasingly focusing on phytopharmaceuticals, with advancements in extraction, standardization, and clinical trials of plant-based products.

Collaborations between traditional healers and modern scientists can boost innovation and help in developing evidence-based phytopharmaceuticals that meet global regulatory standards. India is one of the largest exporters of herbal and plant-based products, with a significant focus on phytopharmaceuticals. The demand for plant-based medicines in Europe, North America, and South-east Asia has grown due to increasing interest in natural therapies.

2.5. Regulatory framework

- The Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homeopathy) was established in 2014 to promote traditional medicine and oversee the development of herbal drugs, including phytopharmaceuticals (6).
- The Indian government developed guidelines for the approval of phytopharmaceuticals, which included parameters for clinical trials, toxicity studies, and quality control.
- In 2015, the Drugs and Cosmetics Rules were amended to introduce the concept of phytopharmaceutical drugs. Under these guidelines, plant-based medicines that have undergone clinical trials and are proven to be effective can be marketed as phytopharmaceuticals, distinguishing them from traditional herbal remedies (7).
- GMP and Standardization: The government has made it mandatory for companies producing phytopharmaceuticals to follow Good Manufacturing Practices (GMP) which ensures that the drugs are safe, effective, and of high quality.

3. Government initiatives and support

The Indian government has launched several initiatives to promote the development of phytopharmaceuticals, recognizing their immense potential for healthcare and the pharmaceutical industry. Key initiatives and support mechanisms include:

3.1. AYUSH ministry

The Ministry of Ayurveda, Yoga, Unani, Siddha, and Homeopathy (AYUSH) plays a significant role in promoting traditional systems of medicine, including phytopharmaceuticals. Through this ministry, the government supports research, standardization, and the commercialization of plant-based medicines.

3.2. National Medicinal Plants Board (NMPB)

Established under the Ministry of AYUSH, the NMPB promotes the cultivation and sustainable use of medicinal plants. It provides financial assistance to farmers and entrepreneurs for the cultivation, conservation, and development of medicinal plants used in phytopharmaceuticals (8).

3.3. Phytopharmaceuticals guidelines (2015)

The Central Drugs Standard Control Organization (CDSCO) introduced specific guidelines for phytopharmaceutical drug development, making it easier for companies to bring plant-based medicines to the market (9). These guidelines streamline the process for conducting clinical trials and getting regulatory approvals.

3.4. Biotechnology Industry Research Assistance Council (BIRAC)

BIRAC, under the Department of Biotechnology, provides funding for research and innovation in phytopharmaceuticals. It supports startups and research organizations working on novel plant-based formulations (10).

These initiatives aim to boost research, cultivation, and commercialization of phytopharmaceuticals, positioning India as a global leader in the sector.

4. Modern trends and global impact

Modern trends in phytopharmaceuticals, driven by advancements in technology and a growing preference for natural therapies, are significantly impacting global healthcare. India, with its rich biodiversity and traditional medicinal knowledge, stands to benefit immensely from these trends.

4.1. Increasing research on bioactive compounds

India's focus on the scientific validation of traditional herbal medicines has led to the discovery of new bioactive compounds with potential therapeutic uses. This includes research into compounds like curcumin (from turmeric), withanolides (from ashwagandha), and bacosides (from brahmi), which have shown potential in treating conditions like cancer, Alzheimer's disease, and inflammation (11).

4.2. Global interest

India’s expertise in medicinal plants has attracted global interest in phytopharmaceutical R&D. Collaborations between Indian companies and international pharmaceutical giants have increased to explore plant-based therapies for chronic diseases (12).

4.3. Growing global market

The global market for phytopharmaceuticals is expected to grow significantly, driven by increasing consumer preference for natural medicines. India can tap into this demand, particularly in areas such as chronic diseases, lifestyle disorders, and immune support.

The global herbal medicine market size was valued at USD 216.40 billion in 2023 and is projected to grow from USD 233.08 billion in 2024 to USD 437 billion by 2032, exhibiting a CAGR of 8.17% during the forecast period.

Europe dominated the herbal medicine market with a market share of 44.82% in 2023. Moreover, the herbal medicine market size in the U.S. is projected to grow significantly, reaching an estimated value of USD 37.90 billion by 2032, driven by growing consumer awareness about health (13).

India contributes significantly to the global supply of medicinal plants and phytopharmaceutical products. Its herbal exports stood at USD 539.57 million in 2022, making it a key player in the global market.

Several well-known phytopharmaceutical products have gained international recognition for their therapeutic benefits. These products are derived from plant-based compounds and are used in various healthcare applications (Table 1).

Table 1. Details of well-known phytopharmaceuticals in the market

Marketed Product	Uses	Brand Name
Silymarin (Milk Thistle)	Primarily used for liver diseases, including cirrhosis, hepatitis, and liver damage from alcohol and toxins (14).	Legalon, Silibinin, Siliphos.
Curcumin (Turmeric)	Known for its anti-inflammatory, antioxidant, and potential anti-cancer properties (15).	Meriva, Curcumin C3 Complex.

Artemisinin (Sweet Wormwood)	The primary active component in the treatment of malaria. (16).	Coartem (artemether and lumefantrine combination), Riamet.
Vinpocetine	Used for improving cognitive functions and treating cerebrovascular disorders like stroke and memory issues (17).	Cavinton, Vinpo-10.
Forskolin *(Coleus forskohlii)*	Popular in weight management supplements and as a treatment for glaucoma, asthma, and cardiovascular conditions (18).	ForsLean.
Boswellia serrata (Indian Frankincense)	Known for anti-inflammatory and anti-arthritic properties (19).	Shallaki, Boswellin.
Cannabidiol (CBD)	Widely marketed for treating epilepsy (e.g., Dravet syndrome), pain, anxiety, and other conditions (20).	Epidiolex (FDA-approved), Charlotte's Web.
Andrographis paniculata (Kalmegh)	Used in respiratory infections, liver issues, and immune system support. (21).	KalmCold,Kan Jang.
Ginkgo biloba	Mainly marketed for cognitive improvement, memory enhancement, and circulatory disorders (22).	Tebonin,Ginkgold.
Quinine (Derived from Cinchona Bark)	Traditionally used for treating malaria (23).	Quinate, Qualaquin.
Resveratrol	Promoted for cardiovascular health, anti-aging, and antioxidant benefits (24)	Longevinex.
Ashwagandha (*Withania somnifera)*	Adaptogen used for stress relief, cognitive function, and improving vitality (25).	Sensoril, KSM-66.
Picroliv *(Picrorhiza kurroa)*	Used for liver protection and boosting immune responses (26).	Liv-52, Picroliv

5. Challenges

Phytopharmaceuticals hold immense potential for India's healthcare and pharmaceutical sectors, but several challenges hinder their growth. One of the key issues is standardization. Variability in the composition of plant-based medicines, influenced by factors like geographical location, season, and cultivation practices, leads to inconsistent therapeutic outcomes (27). This complicates product

approval, as regulatory bodies require strict adherence to quality standards, efficacy, and safety, comparable to synthetic drugs.

Another challenge is scientific validation. Unlike conventional pharmaceuticals, phytopharmaceuticals often lack extensive clinical data. The absence of robust clinical trials and comprehensive toxicological studies limits their acceptance among healthcare professionals and international markets (28).

Additionally, complex regulatory frameworks act as a barrier. India's regulations for phytopharmaceuticals, though evolving, remain less streamlined compared to Western countries. The regulatory landscape needs clearer guidelines to support product development and commercialization while ensuring quality and safety. Finally, intellectual property (IP) issues present challenges. Many phytopharmaceuticals are based on traditional knowledge, making patenting difficult under current legal frameworks. This restricts the development of proprietary formulations and investments in research.

Overcoming these challenges through better standardization, clinical validation, and supportive regulatory frameworks could help unlock the full potential of phytopharmaceuticals in India.

6. Conclusion

India's journey from traditional herbal remedies to modern phytopharmaceuticals reflects the country's ability to integrate ancient knowledge with modern science. Today, India is a leader in phytopharmaceutical production, with a robust regulatory framework that ensures the quality and efficacy of plant-based drugs. This sector holds great potential for addressing modern health challenges using natural resources. Phytopharmaceuticals offer immense potential for India in terms of healthcare solutions, economic growth, and exports. With a combination of its rich biodiversity, traditional knowledge, and increasing focus on R&D, India is well-positioned to become a global leader in the phytopharmaceutical industry.

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Phytopharmaceuticals for brain disorders: An Indian perspective

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Abstract
The increasing prevalence of central nervous system (CNS) disorders in India, including neurodegenerative diseases like Alzheimer's and Parkinson's, alongside mental health issues such as depression and anxiety, presents a significant health challenge. Traditional Indian medicinal plants, including *Bacopa monnieri, Withania somnifera, Centella asiatica,* and *Curcuma longa,* demonstrate promising neuroprotective and cognitive-enhancing effects supported by both preclinical and clinical evidence. However, their therapeutic application is hindered by challenges such as poor solubility, limited blood-brain barrier permeability, rapid metabolism, and stability concerns. To address these issues, innovative formulation strategies, including nanoformulations and prodrugs, are being investigated to improve bioavailability and efficacy. By combining traditional knowledge with modern pharmaceutical approaches, Indian phytopharmaceuticals have the potential to offer effective, safe, and affordable treatments for CNS disorders, enhancing the quality of life for those affected.

Keywords: Phytopharmaceuticals, Central nervous system (CNS) Disorders, Neurodegenerative diseases

1. Introduction
CNS disorders, including neurodegenerative diseases, psychiatric conditions, and neurological disorders, are on the rise in India, significantly contributing to the national health burden. The prevalence of these disorders is alarming due to increasing life expectancy, lifestyle changes, and other contributing factors:

- **Neurodegenerative disorders**: India is witnessing a surge in cases of neurodegenerative diseases such as Alzheimer's and Parkinson's disease. For instance, Alzheimer's disease affects about 4 million people in India, with the number expected to rise as the population ages. Parkinson's disease prevalence is also increasing, with estimates suggesting around 300,000 to 400,000 individuals currently affected (1,2).
- **Psychiatric conditions:** Mental health disorders such as depression, anxiety, bipolar disorder, and schizophrenia are becoming more common. According to the National Mental Health Survey (2015-16), nearly 150 million Indians require mental health interventions, with depression affecting over 45 million people (3).

- **Neurological disorders:** Epilepsy is one of the most common neurological conditions in India, affecting about 10 million people. Stroke, another major neurological disorder, has also become more prevalent due to risk factors such as hypertension and diabetes (4,5).

2. Traditional Indian medicinal plants with CNS activity

Bacopa monnieri (Brahmi) is a renowned brain tonic used to enhance memory, reduce anxiety, and protect neurons from oxidative stress, making it a candidate for treating neurodegenerative diseases (6).*Withania somnifera* (Ashwagandha) is an adaptogen that reduces stress, anxiety, and depression, while also improving cognitive function and offering neuroprotection (7). *Centella asiatica* (Gotu Kola) is used to enhance memory, reduce anxiety, and protect against neuroinflammation (8). *Nardostachys jatamansi* (Jatamansi) has sedative properties and is effective in treating insomnia, epilepsy, and depression (9). *Convolvulus pluricaulis* (Shankhpushpi) is a cognitive enhancer that helps reduce anxiety and oxidative damage in the brain (10). *Mucuna pruriens* (Velvet Bean), rich in L-DOPA, is used to manage Parkinson's disease and depression (11). *Curcuma longa* (Turmeric) is valued for its anti-inflammatory and antioxidant effects, improving cognitive function and memory while preventing neurodegeneration (12). *Acorus calamus* (Vacha) is known for its calming and anti-epileptic properties, promoting mental clarity and reducing stress. These plants hold immense potential for developing phytopharmaceuticals targeting CNS disorders (13).

3. Preclinical and clinical evidence for Indian phytopharmaceuticals in CNS disorders

3.1. *Bacopa monnieri* (Brahmi)

- **Preclinical evidence:** Animal studies have shown that *Bacopamonnieri* possesses strong neuroprotective and cognitive-enhancing properties. It improves spatial memory, reduces oxidative stress, and modulates neurotransmitters like acetylcholine. Studies on rodents demonstrated that Bacopa reduces cognitive deficits induced by Alzheimer's disease models, supporting its role in neuroprotection.
- **Clinical evidence:** Several randomized controlled trials (RCTs) have demonstrated Bacopa's efficacy in improving memory and cognitive function in healthy adults and elderly populations. A clinical study on elderly individuals with age-associated memory impairment showed significant improvements in memory retention and learning. Another trial found Bacopa to reduce anxiety and improve cognitive processing speed in healthy subjects (14).

3.2. *Withania somnifera* (Ashwagandha)

- **Preclinical evidence:** Ashwagandha has demonstrated anti-anxiety, anti-depressant, and neuroprotective effects in preclinical models. Animal studies have shown that it can reduce stress by regulating cortisol levels and enhancing resilience to chronic stress. It also supports neurogenesis and has potential benefits in treating neurodegenerative diseases such as Alzheimer's and Parkinson's.
- **Clinical evidence:** Ashwagandha has shown promising results in clinical trials for reducing stress and anxiety. In one study, patients with anxiety disorders experienced a significant reduction in anxiety and serum cortisol levels after treatment with Ashwagandha extract. In trials involving cognitive function, it was shown to improve memory, attention, and information processing in individuals with mild cognitive impairment (15).

3.3. *Centella asiatica* (Gotu Kola)

- **Preclinical evidence**: Gotu Kola has been extensively studied for its neuroprotective, cognitive-enhancing, and anxiolytic effects. Animal studies indicate that it enhances learning and memory in Alzheimer's models by reducing beta-amyloid toxicity and oxidative stress in the brain. Its antioxidant properties help protect against neuronal damage.
- **Clinical evidence:** In clinical studies, Gotu Kola has shown improvements in cognitive function and anxiety reduction. A study involving elderly patients with cognitive decline demonstrated enhanced memory and learning. Another clinical trial found Gotu Kola to be effective in reducing anxiety in patients with generalized anxiety disorder (GAD) (16).

3.4. *Nardostachys jatamansi* (Jatamansi)

- **Preclinical evidence:** Animal studies have indicated that Jatamansi has sedative, anti-depressant, and anti-convulsant properties. It modulates serotonin and GABA levels in the brain, offering potential benefits for epilepsy, insomnia, and anxiety. Preclinical models of depression have shown that Jatamansi alleviates symptoms by modulating neurotransmitter levels.
- **Clinical evidence:** Although clinical studies are limited, Jatamansi has been traditionally used for its calming effects. Preliminary human studies suggest that it may improve sleep quality and reduce symptoms of anxiety. Further clinical trials are needed to establish its efficacy in CNS disorders (17).

3.5. *Convolvulus pluricaulis* (Shankhpushpi)

- **Preclinical evidence:** Shankhpushpi has shown promising results in animal studies as a cognitive enhancer and neuroprotective agent. It has been found to improve memory and learning in animal models of cognitive impairment and Alzheimer's disease by modulating cholinergic activity and reducing oxidative stress.
- **Clinical evidence**: While clinical evidence is still emerging, some studies have demonstrated the potential of Shankhpushpi in enhancing memory and cognitive performance in both healthy adults and patients with cognitive decline. Clinical trials have also shown its anxiolytic effects, helping reduce symptoms of stress and anxiety (18).

3.6. *Mucuna pruriens* (Velvet Bean)

- **Preclinical evidence**: *Mucunapruriens* is well-known for its high content of L-DOPA, which is a precursor to dopamine. Preclinical studies have demonstrated its neuroprotective effects in Parkinson's disease models, where it protects dopaminergic neurons and improves motor function. It has also shown anti-depressant effects in preclinical models.
- **Clinical evidence:** Clinical trials have confirmed the efficacy of Mucuna in managing Parkinson's disease. A study comparing *Mucunapruriens* with standard L-DOPA treatment found it to be more effective in improving motor function and with fewer side effects. Additionally, its neuroprotective effects suggest a potential for long-term benefits in Parkinson's patients (19).

3.7. *Curcuma longa* (Turmeric)

- **Preclinical evidence:** Curcumin, the active component of turmeric, has been shown to have strong anti-inflammatory, antioxidant, and neuroprotective properties in preclinical models of neurodegenerative diseases like Alzheimer's and Parkinson's. It reduces beta-amyloid plaques, oxidative stress, and neuroinflammation, key contributors to cognitive decline.
- **Clinical evidence:** Clinical studies have found curcumin to improve memory and attention in elderly patients with mild cognitive impairment. One RCT demonstrated that curcumin supplementation improved cognitive function in healthy older adults. Furthermore, studies have shown its efficacy in reducing depressive symptoms and improving mood, likely due to its impact on serotonin and dopamine levels (20).

3.8. *Acorus calamus* (Vacha)

- **Preclinical evidence:** Vacha has demonstrated neuroprotective, anti-epileptic, and cognitive-enhancing properties in animal models. Preclinical studies suggest that it may reduce seizure activity and improve memory by modulating neurotransmitter levels, particularly acetylcholine and GABA.
- **Clinical evidence:** Clinical evidence for Vacha is limited, but its traditional use in Ayurveda for treating epilepsy, anxiety, and cognitive decline is well-documented. Further research is needed to validate its therapeutic potential in human clinical trials (21).

Table 1. Medicinal plants and their bioactive compounds in the management of CNS disorders: parts used, bioactive constituents, and mechanisms of action

Plant	Part Used	Bioactive Constituents	CNS Disorder Type	Mechanism of Action
Bacopa monnieri	Leaves	Bacosides, Alkaloids	Alzheimer's, Memory Disorders	Antioxidant, modulates acetylcholine levels, reduces oxidative stress (22)
Withania somnifera	Roots	Withanolides, Sitoindosides	Anxiety, Depression, Alzheimer's	Modulates cortisol levels, neurogenesis support, reduces neuroinflammation (23)
Centella asiatica	Whole Plant	Asiaticoside, Madecassoside	Cognitive Decline, Anxiety	Antioxidant, reduces beta-amyloid toxicity, neuroprotective properties (24)
Nardostachys jatamansi	Rhizomes	Sesquiterpenes, Valeranone	Insomnia, Epilepsy, Depression	Sedative, anti-convulsant, modulates serotonin and GABA (25)
Convolvulus pluricaulis	Whole Plant	Convolvamine, Scopoletin	Anxiety, Cognitive Disorders	Enhances cholinergic activity, reduces oxidative stress (26)
Mucuna pruriens	Seeds	L-DOPA	Parkinson's, Depression	Increases dopamine levels, neuroprotection for dopaminergic neurons (27)
Curcuma longa	Rhizomes	Curcumin	Alzheimer's, Cognitive Impairment	Anti-inflammatory, reduces beta-amyloid plaques, antioxidant effects (28)
Acorus calamus	Rhizomes	α-Asarone, β-Asarone	Epilepsy, Anxiety	Modulates acetylcholine and GABA levels, anti-epileptic properties (29)

4. Formulation challenges and bioavailability

Phytopharmaceuticals offer significant therapeutic potential for CNS disorders but face several formulation challenges that impact their bioavailability. Key issues include poor solubility, which limits absorption; difficulty crossing the blood-brain barrier (BBB); rapid metabolism leading to short half-lives; and stability concerns due to degradation from light, heat, and oxygen. To overcome these obstacles, various formulation strategies are employed. Nanoformulations, such as nanoparticles, nanoemulsions, and solid lipid nanoparticles, enhance solubility and permeability, improving absorption and BBB transport. Surface modification of nanocarriers can facilitate targeted delivery to the brain, while intranasal delivery methods provide direct access to CNS pathways. Prodrugs and co-administration with bioenhancers, like piperine, can help extend the half-life of phytochemicals.

Additionally, encapsulation in biodegradable polymers aids in stabilizing these compounds and providing sustained release. Despite these challenges, ongoing research aims to enhance the efficacy and bioavailability of Indian phytopharmaceuticals for CNS applications, making them promising candidates for future therapeutic development (30,31).

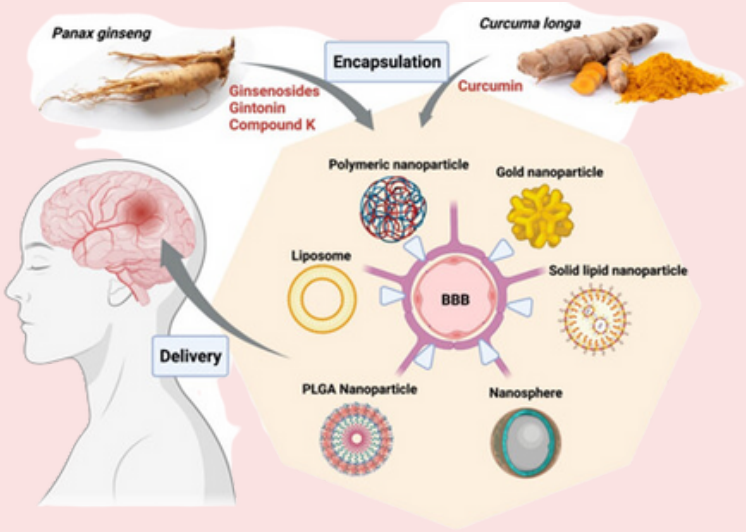

Figure 1. Nanoparticles of phytoconstituents for various CNS disorders

5. Conclusion

Indian phytopharmaceuticals hold significant promise for treating Central Nervous System (CNS) disorders, supported by both traditional practices and scientific research. Key medicinal plants like *Bacopamonnieri, Withaniasomnifera, and Curcuma longa* have shown neuroprotective and cognitive-enhancing effects in studies. However, challenges such as poor solubility, limited blood-brain barrier permeability, rapid metabolism, and stability issues hinder their therapeutic application. Innovative formulation strategies, including nanoencapsulation and the use of prodrugs and bioenhancers, are being explored to improve bioavailability and efficacy. The combination of traditional knowledge with modern pharmaceutical techniques has the potential to develop effective, safer, and more affordable treatments for CNS disorders, ultimately enhancing the quality of life for many affected individuals.

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Beyond chemotherapy: The therapeutic promise of plant-derived compounds in cancer treatment



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Abstract

Cancer is the second leading cause of death worldwide. Despite significant advancements in treatment and control, there remain critical deficiencies and opportunities for improvement. Chemotherapy often comes with undesirable side effects, prompting interest in natural therapies, particularly plant-derived products, which may help mitigate these adverse effects. Currently, a limited number of plant products are utilized in cancer treatment, yet numerous others exhibit promising anticancer properties in vitro but have not yet been evaluated in humans. Further research is essential to assess the efficacy of these plant compounds for cancer treatment in clinical settings. This review will focus on various plant-derived chemical compounds that have recently shown potential as anticancer agents, detailing their mechanisms of action and the promise they hold for future therapeutic development.

Keywords: Phytoconstituents, Cancer, Natural Compounds

1. Introduction

Phytoconstituents, derived from plants, are increasingly being explored as adjuncts or alternatives in cancer treatment. Their potential benefits include enhancing the efficacy of conventional therapies, reducing side effects, and improving patients' quality of life.

Emerging cancer treatment strategies are shifting from solely cytotoxic approaches to more holistic methods that focus on managing cancer physiopathology. These integrative approaches aim not just to eradicate affected cells but to control the overall cancer phenotype. Numerous plant-derived products have demonstrated promise in anticancer therapies, with efforts made to characterize the effectiveness of individual constituents isolated from natural sources as chemopreventive agents.

In this context, Ayurveda, with its holistic treatment philosophy, offers a valuable alternative to isolated plant compounds. This ancient system of medicine incorporates a variety of herbs into treatment regimens for numerous diseases. The foundational texts of Ayurveda, such as the Charaka Samhita and Sushruta Samhita, dating back to approximately 1000 B.C., document the use of plant products in disease treatment. These texts describe cancer as either inflammatory or non-inflammatory swellings, referred to as Granthi (minor neoplasm) or Arbuda (major neoplasm) (1).

Phytoconstituents used in cancer treatment offer several advantages over conventional therapies, such as chemotherapy and radiation, due to their unique mechanisms, generally lower toxicity, and multi-targeted effects (Depicted in figure 1).

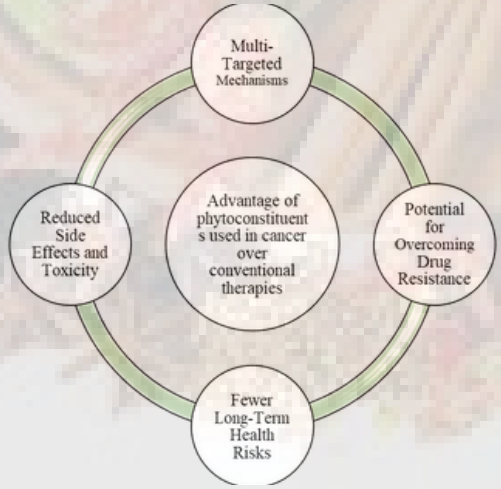

Figure 1. Advantage of phytoconstituents used in cancer

For example, *Tinospora cordifolia* is recognized for its anti-inflammatory and anticancer properties. In vitro studies have shown its potential against cancer cells. Similarly, *Andrographis paniculata* extracts exhibit anti-oncogenic effects, while oral administration of *Centella asiatica* extracts has been reported to slow tumor development and extend lifespan in tumor-bearing mice. Turmeric has also demonstrated the ability to inhibit tumor cell invasion and metastasis in vitro. Moreover, *Phyllanthus amarus* extracts significantly increased lifespan and reduced tumor size in models of Dalton's lymphoma ascites and Ehrlich ascites carcinoma (2).

Table 1. Anticancer activities of major chemical constituents of medicinal plants

Name of Plant	Major Chemical Constituents	*In Vivo* Effects	Ref
Tinospora cordifolia	20 β-hydroxyecdysterone, Cordioside, Columbin	*Tinospora cordifolia,* containing compounds like 20 β-hydroxyecdysterone, cordioside, and columbin, has demonstrated significant tumor regression and increased survival in mice with Ehrlich ascites carcinoma	(3)
Andrographis paniculata	Andrographolide	*Andrographis paniculata,* with its active compound andrographolide, has been shown to regress tumors in mice	(4)
Curcuma longa	Curcumin	*Curcuma longa*, containing curcumin, reduces VEGF and bFGF-mediated angiogenesis and prevents colon and gastric cancers in rodent models. These effects underscore curcumin's potential as a cancer-preventive agent	(5,6)
Phyllanthus amarus	Nirtetralin, niranthrin, phyllanthin, phyltetralin	*Phyllanthus amarus,* containing compounds like nirtetralin, niranthrin,phyllanthin, and phyltetralin, increases lifespan and reduces tumor size in mice with Dalton's lymphoma ascites (DLA) and Ehrlich ascites carcinoma (EAC). Additionally, it decreases N-nitrosodiethylamine (NDEA)-induced tumor incidence and exhibits anti-angiogenic effects in mice with Lewis lung carcinoma	(7-9)
Mappia foetida	Camptothecin	Induces partial or complete remission of breast carcinoma in the xenograft model system	(10,11)
Withania somnifera	Withaferin A	*Withania somnifera*, particularly withaferin A, is highly effective in producing over 50% tumor regression in Ehrlich ascites carcinoma (EAC) and Ehrlich ascitic tumor (EAT) models. Additionally, it enhances Th1 cytokine expression and increases T cell and CD40 expression in the EAT mouse tumor model, indicating its potential to boost immune response against tumors	(12)
Cedrus deodara	Lignans, Wikstromol, Matairesinol and dibenzyl butyrolactol	*Cedrus deodara,* containing lignans like wikstromol, matairesinol, and dibenzyl butyrolactol, demonstrates tumor regression in murine models	(13)
Boswellia serrata	Triterpenic acids	*Boswellia serrata,* rich in triterpenic acids, has shown effectiveness against brain tumors. This highlights its potential therapeutic application in treating neurological cancers	(14)

2. Current status of Phytoconstituents in cancer

2.1. Research and development

- **Active compounds:** Many plant-based compounds, such as curcumin (from turmeric), resveratrol (from grapes), and various alkaloids (like paclitaxel from the yew tree), are under investigation for their anticancer properties (15).
- **Mechanisms of action:** These compounds may work through various mechanisms, including apoptosis induction, anti-inflammatory effects, and inhibition of tumor angiogenesis.

2.2. Clinical trials

- **Combination therapies:** Clinical trials are increasingly testing combinations of Phytoconstituents with standard treatments (chemotherapy, radiotherapy) to assess synergistic effects (16).
- **Patient-centric studies:** Trials focus on quality of life improvements, symptom management, and survivorship outcomes (17).

2.3. Regulatory approval

- **Standardization challenges:** One of the significant hurdles is the lack of standardization and quality control in the production of phytoconstituents, making it difficult to ensure consistent therapeutic effects (18).
- **Regulatory framework:** Some phytoconstituents have gained approval in specific regions (e.g., Europe) for certain indications, but many remain classified as dietary supplements rather than drugs (19).
  1. The European Medicines Agency (EMA) has a specific pathway for herbal medicinal products under the Committee on Herbal Medicinal Products (HMPC).
  2. The FDA regulates many phytoconstituents as dietary supplements rather than drugs, which requires that they meet safety standards but do not need to demonstrate efficacy.
  3. The WHO has issued guidelines to support regulatory bodies in developing standards for traditional medicines, though specific regulations vary widely across countries.
  4. Traditional medicine systems like Ayurveda are recognized within national frameworks, with specific regulatory bodies overseeing herbal medicines.
  5. Kampo medicines, which are herbal formulations based on traditional Japanese medicine, are regulated as pharmaceuticals. Kampo products must meet strict quality and safety standards, and specific indications are approved based on clinical efficacy data.

2.4. Integrative oncology

- **Holistic approach:** There's a growing trend in integrative oncology that combines conventional cancer treatments with complementary therapies, including Phytoconstituents, focusing on the overall well-being of patients (20).

3. Future directions

- **Personalized medicine:** Research is moving towards understanding how individual genetic and metabolic profiles can affect the efficacy of phytoconstituents, aiming for more personalized cancer treatment strategies.
- **Ongoing studies:** New studies continue to emerge, examining the potential of various plants and their extracts in different cancer types.

4. Conclusion

This review revelled that phytoconstituents and its products possess antitumor activity with lesser side effect. It has to required isolation of plants constituents that may lead to discovery of novel anticancer agents.

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Unravelling the therapeutic potential of *Lantana camara* in skin cancer


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Abstract

Natural products and their metabolites have a historical significance as they serve as a starting point for drug discovery and development process. *Lantana camara*, a notorious invasive weed has been used in folk medicine for managing various health concerns. Pentacyclic triterpenoids (Lantadenes), have attracted significant interest due to their anticancer potential. The present study include *in vivo* anticancer investigations of 3β-(4-Methoxybenzoyloxy)-22β-senecioyloxy-olean-12-en-28-oic acid using two-stage carcinoma model. This compound showed notable anticancer potential, evidenced by a substantial reduction in tumour burden and volume along with attenuation in proliferation, thickness, and corrugation of epidermis in cancer model. These findings indicate Lantadene structural modification may hold substantial potential against skin malignancies.

Keywords: Lantadenes, Weed, Natural products, Anticancer

1. Introduction

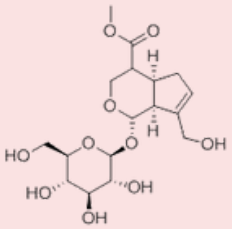
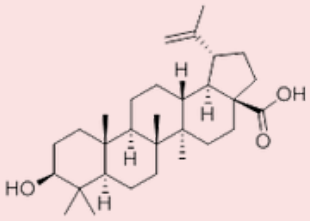
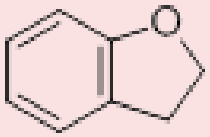
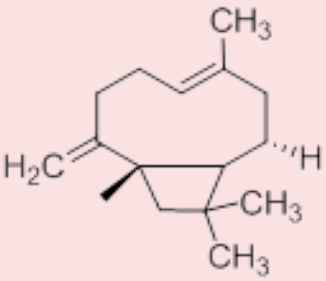
Mother nature serves as an endless reservoir for new chemotypes and pharmacophores. Natural metabolites and their derivatives have historically made a major contribution in pharmacotherapy, specifically in infectious and cancer diseases (1,2). Natural product (NP) databases exemplifies structural and qualitative activity information for approximately 4,70,000 NPs, while around 5,000 NPs are reported with experimental values only, highlighting a significant untapped profile of natural products (3,4). The use of natural products for medical purposes is dated back dawn to human existence. The utilization of plants as therapeutic agents is even evidenced by the murals found in the Lascaux caves, dated back to 20,000 B.C. (5).

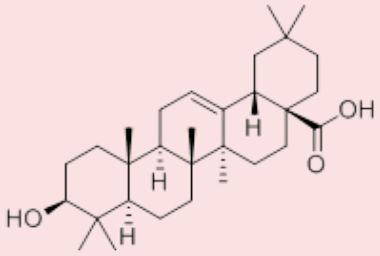
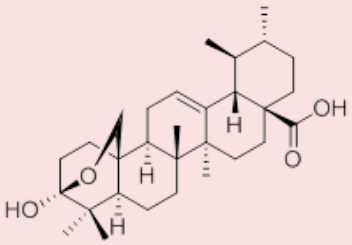
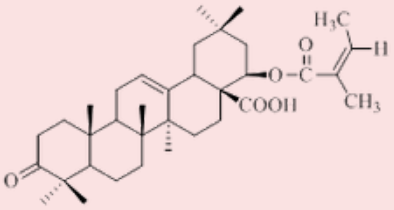
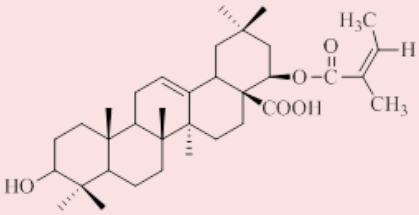
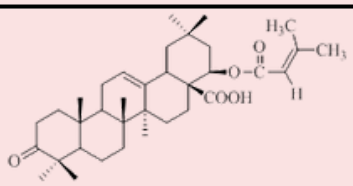
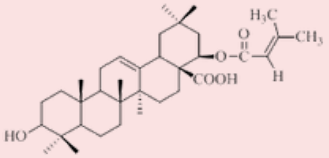
Plants provide an extensive chemical space filled with therapeutic potential, and emerging as a topic of global significance in drug discovery process. Plant-derived metabolites have significantly contributed in the treatment of numerous ailments (6). The potential benefits of these secondary metabolites are owed to their remarkable stereochemistry, structural diversity and extensive range of pharmacophore enhances receptor binding selectivity, offering these natural scaffolds as a valuable source for novel pharmaceuticals (7). As far as plants are concerned, the significance of weeds in the pharmacopoeia has been under-valued despite of strong evidence that weeds are being used as medicines among indigenous people (8). Numerous investigations have indicated that weeds are rather rich in secondary metabolites, hence they may have great potential for therapeutic development (9).

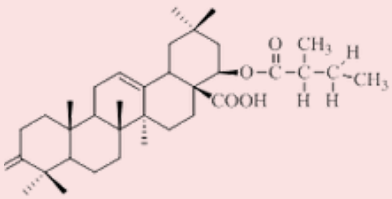
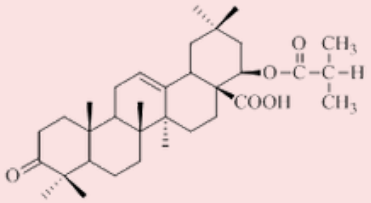
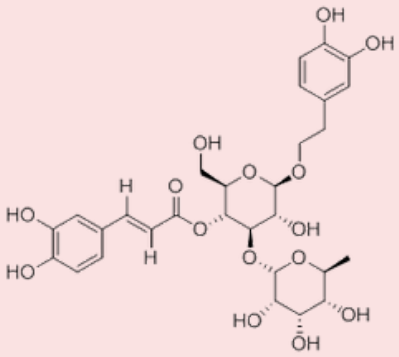
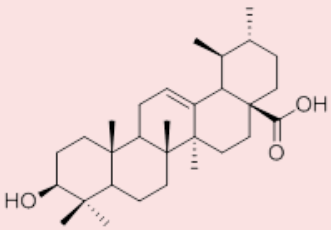
Lantana camara, a member of the Verbenaceae family, is a notorious weed that has attracted significant attention among the scientists since the last two decades (10). *Lantana camara*, also known as red sage, wild sage or lantana, is considered as one of the most noxious weeds globally (11). Linnaeus created the genus Lantana in 1753, and Chamisso subsequently defined the subgenus Camara in 1832 (12). Lantana is indigenous to tropical & subtropical America being distributed across 60 nations and reported with approximately 650 varieties (13).

During early 1690s, Lantana began to spread across the entire world through trade and commerce. According to Kohli et al., first time Lantana was brought to India during 1807 in Kolkata, while introducing variety of plants to the botanical gardens (14). Further, the modern medical system has started to acknowledge the beneficial effects of Lantana (15). Lantana has been extensively reported for its potential as anti-cancer, anti-ulcer, anti-malarial, anti-microbial, nematicidal, anti-hyperglycaemic, wound healing potentials, and anti-hypertensive etc. shown in Table 1.

Table 1. Phytochemicals from *Lantana camara* and their pharmacological activity.

Plant parts	Phytochemical	Pharmacological activity	Ref
Roots	 Geniposide	Hypolipidemic activity	(15)
Aerial parts, stem	 Betulinic acid	Anti-leishmanial, cytotoxic, nematicidal activity	(16)
Leaves	 Coumaran	Insecticidal, Anti-acetylcholinesterase activity	(17)
Leaves	 *E*-Caryophyllene	Bactericidal, anti-fungal, antimicrobial, anticancer activity	(18)

Aerial parts, stem, roots	 Oleanolic acid	Antiurolithiatic antimicrobial, hepatoprotective,anti-inflammatory, antihyperlipidemic, antifertility, antimicrobial,antiulcer, nematicidal activity	(19-21)
Leaves	 Lantic acid	Antibacterial activity	(22)
Stem, leaves, roots	 Lantadene A	Anti-leshmanial, Nematicidal, anti-microbial, antitubercular, anti-cancer activity	(23-25)
Leaves	 Reduced Lantadene A	Antiviral, cytotoxic activity	(12,26)
Stem, leaves	 Lantadene B	Antiviral, hepatotoxicity, nematicidal antimicrobial, allelopathy, antitumor activity	(27,28)
Leaves	 Reduced Lantadene B	Anticancer potential	(12,26)

Stem, leaves,	 Lantadene C	Antiviral activity	(28)
Stem	 Lantadene D	Anticancer activity	(23)
Stem, leaves	 Verbascoside	Vasodilator, antifungal, Cardiotonic, protein kinase C inhibitor,antihypertensive, anti-inflammatory, anticancer	(29)
Leaves	 Urs-12-en-3β-ol-28-oic acid 3β-D-glucopyranosyl-4-octadecanoate	Anti-diabetic activity	(30)

Pentacyclic terpenoids, specifically Lantadene A and B (Figure1), have garnered significant interest due to their promising cytotoxic properties. Over the past decade, various structural modifications were implemented at C-2, C-3, C-17, C-22 positions in rings A and D, demonstrating anti-inflammatory and anti-tumor properties via downregulation of B-cell lymphoma-2, Nuclear factor kappa B, c-Jun, and the inhibition of Akt protein (27,28). Research from Sharma et al indicated by keeping ester side chain at C-22 and modifying structural variations at C-3 position of Lantadene analogues, revealed significant anti-cancer potential. The remarkable anticancer impact of these compounds is attributed to the predicted binding association of the C-22 ester linkage with the binding domain of receptor that modulate the physiological response (28,31).

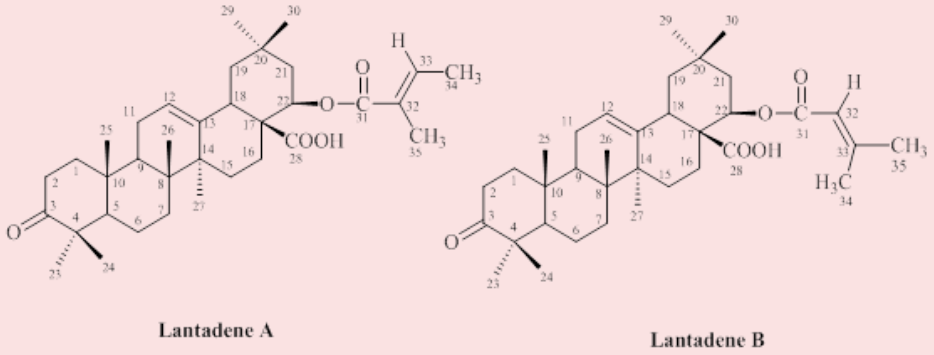


Figure 1. Lantadenes

Exploiting *in silico* studies, we have disclosed 2 & 3 Dimensional quantitative structure-activity relationship investigations, highlighting pharmacophoric features that govern anti-cancer potential (31). Subsequently collective *in vitro* & *in silico* analysis of our recently published research article on synthesis of C-3 ester analogues of Lantadenes have identified 3β-(4-Methoxybenzoyloxy)-22β-senecioyloxy-olean-12-en-28-oic acid, as a lead molecule (32). Thus the current study, attempted to investigate anti-cancer efficacy of 3β-(4-Methoxybenzoyloxy)-22β-senecioyloxy-olean-12-en-28-oic acid in model of skin carcinogenesis.

2. Experimental

2.1. *In vivo* studies

The anti-cancer activity of 3β-(4-Methoxybenzoyloxy)-22β-senecioyloxy-olean-12-en-28-oic acid was evaluated in Swiss albino mice (LACCA) using a skin carcinogenesis (two-stage) model. The Animal Ethics Committee, Panjab University, Chandigarh (PU/45/99/CPCSEA/IAEC/2018/120) evaluated & approved all procedures for *in vivo* studies and CPCSEA standards were followed for animal care, handling, and experimentation. Depilatory lotion was used on the dorsal skin of mice to eliminate hair.

Mice in control (Group I; n=5) served as control and received only acetone (100µL) as vehicle treatment biweekly for 25 weeks. Group II (n=14) animals received 100nmol 7,12-Dimethylbenz[a]anthracene (DMBA) biweekly for 2 weeks, subsequently followed by 1.7nmol 12-O-tetradecanoylphorbol-13-acetate (TPA) administration biweekly for the next 23 weeks. Group III (DMBA/TPA + compound; n=14)animals received 50mg/Kg body weight of mice with 3β-(4-Methoxybenzoyloxy)-22β-senecioyloxy-olean-12-en-28-oic acid from 4 week onwards and continued till 25thweek. After the termination of protocol tumor incidence %, mean tumor volume and burden were analysed. Further, Histoarchitechtural investigation were performed by fixing of skin & tumors samples in Zenker and staining with hematoxylin and eosin dye.

3.Result and discussion

3.1. *In vivo* studies

The topical treatment of DMBA/TPA over 25 weeks led to tumour development, with the exception of control group I. All animals were monitored for lesions, papillomas, and tumours during the treatment. Figure 2 shows various morphological transformations in skin cancer during the protocol. The first appearance of papillomas, average tumor count, and animal mortality were recorded weekly for the period of 25 weeks. Additionally, tumour burden and volume were evaluated at end of protocol. In group II animals, papillomas appeared in the sixth week and progressed from 26 to 100% by eleventh week. On the other hand, group-III animals emerged with 13% at week six and escalated to 53% by the end of the protocol. Administration of compound attenuated tumour incidence by 47% in group III animals compared to group II. Further, results from Table 2 demonstrated the mean tumor volume ranged from 30-716 mm^3 & 17-67 mm^3 in the group-II group-III animals respectively. Treatment with compound indicated a substantial reduction in tumor volume with a maximal volume of 67 mm^3 compared to group II animal.

In the similar direction mean tumor burden was calculated and varied from 67-1431 mm^3 & 15-134 mm^3 for group-II & group-III, respectively. Supporting tumor volume parameter, treatment group significantly decreased tumour burden, with a maximum of 134 mm^3 compared to 1431 mm^3 in group II (Table 2).

Table 2. Impact of 3β-(4-Methoxybenzoyloxy)-22β-senecioyloxy-olean-12-en-28-oic acid on DMBA/TPA induced skin tumors

Parameters	Tumor incidence (%)	Tumor burden (mm^3)	Tumor Volume (mm^3)
Group I	NA	NA	NA
Group II	100%	Range: 67-1431 (766 ± 606)	Range: 30-716 (301±274)
Group III	53%	Range:15-134 (48±45 [b])	Range: 17-67 (31 ± 20 [a])

Data is reported as Mean ± SD (n=14) using Student's t-test. [a]p≤0.01& [b]p≤0.05 significant with respect to group II.

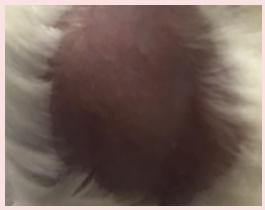
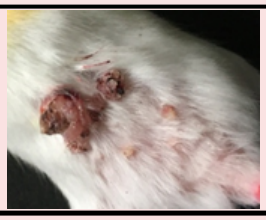
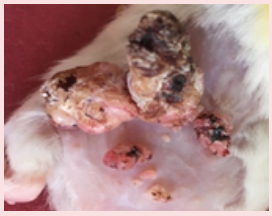
	(Group-II)	(Group-III)
Normal Skin		
1st incidence of lesion at 6th week		
Developing phase during 10th week		
Tumor in the termination stage at 25th week		

Figure 2. Morphological transformations in skin cancer using skin carcinogenesis model

3.2. Histological investigation of normal skin and skin tumours

Histoarchitechtural study was performed on skin samples from group-I and tumor samples from group-II & III tumors. Harvested samples were regularly processed, fixed followed by embedding in Zenker and paraffin respectively. Histopathological examinations were performed under a light microscope using hemoatoxylin and eosin-stained sections.

The administration of DMBA followed by TPA biweekly on bare skin led to tumors development in both group II & group III mice, while no tumors were noticed in the control group. Uniformly arranged intact epidermis, underlying layers & subcutaneous tissues were found in group I samples. Tumours from group II & group III were darkly pigmented with hyperchromatic nuclei, indicating a nucleus-to-cytoplasm ratio favouring the nucleus. Well-defined epidermal carcinoma was identified in group II, characterised by thickened keratinized layer on the epidermis (hyperkeratosis) and corrugated epidermis resulting from hyperproliferation from normal to hyperplastic states. These tumors exhibited a profusion of keratin pearls and substantial infiltration of malignant cells into the underlying dermis, demonstrating a key characteristic of epidermal keratinocyte tumours, specifically squamous cell carcinoma (Figure 3). Histopathological investigation from group III samples verified the existence of squamous cell cancer. Significantly proliferating, corrugated and thickened epidermis was noted. However, epidermis exhibited reduced thickening and markedly decreased keratinisation. Furthermore, vacuoles resulting from degenerative alterations were observed in the tumors retrieved from group III mice. The extent and amount of hyperchromasia was significantly declined in comparison to group II.

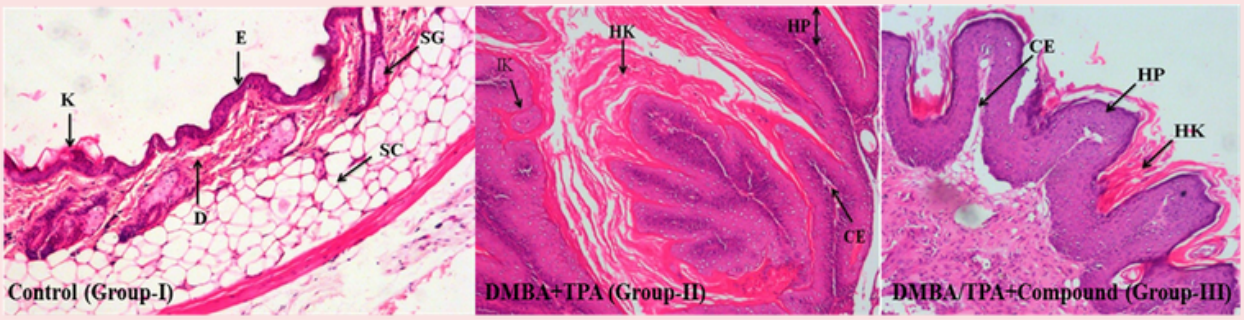


Figure 3. Histoarchitecture samples from group-I, group-II and group-III at 10X magnification: epidermis (E), dermis (D), keratinocytes (K), subcutaneous tissue (SC), Island of epidermal cells encapsulated with keratin (IK), hyperkeratinisation (HK), corrugated epidermis (CE), sebaceous glands (SG), hyperproliferative epidermis (HP).

In vivo investigations indicated that administration of 3β-(4-Methoxybenzoyloxy)-22β-senecioyloxy-olean-12-en-28-oic acid to tumor-bearing mice considerably decreased tumour incidence, indicating chemo preventive action of compound. Further, studies also pointed out that presence of empty spaces in tumours that lead to significant decrease in tumour volume and tumour burden after the treatment may be associated with degrative action of compound.

4. Conclusion

Despite significant advancement, anti-cancer tailored small molecules still suffers from substantial adverse effects. Simultaneously, growing interest in indigenous traditional herbal remedies is emerging as an alternative for the treatment and prevention of various illnesses. Weed Lantana has garnered attention from decades due to its anticancer potential. Observation of this study indicated promising anticancer potential with significant reductions tumour volume, and burden. Further, histopathological investigations revealed attenuation in proliferation, thickness, and corrugation of epidermis indicating 3β-(4-Methoxybenzoyloxy)-22β-senecioyloxy-olean-12-en-28-oic acid as potential candidate against skin cancer. However, additional research is necessary to exhaustively explore the underlying mechanisms and pharmacokinetics studies.

Acknowledgments

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Centella asiatica: Unlocking its health and medicinal benefits in India

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Abstract

Centella asiatica, commonly known as Gotu Kola or Indian Pennywort, is a medicinal herb traditionally used in Ayurvedic, Chinese, and Indonesian medicine for its diverse therapeutic benefits. Rich in bioactive compounds such as triterpenoids, flavonoids, and phenolic acids, C. *asiatica* demonstrates antioxidant, anti-inflammatory, antimicrobial, and wound-healing properties. Its applications range from enhancing skin health by promoting collagen synthesis and hydration to neuroprotection, cardiac health, and digestive support. By regulating inflammation and oxidative stress, it supports cellular health across multiple systems. Notably, its minimal side effects make it a valuable component in natural medicine and cosmetic formulations.

Keywords: Antioxidant, Anti-inflammatory, UV protection, Mitoprotective agent.

1. Introduction

Centella asiatica (CA) (Linn.) Urban synonym *Hydrocotyle asiatica* Linn. commonly known as Indian Pennywort, belongs to the family Apiaceae (previously known as Umbelliferae) (1). *Centella asiatica*, commonly known as Gotu Kola, is a perennial herbaceous plant recognized for its wide range of medicinal properties. Traditionally used in Ayurvedic, Chinese, and Indonesian medicine, this plant is acclaimed for its therapeutic benefits. Its applications span across various domains, particularly in skin care, however, antioxidant, antimicrobial, anti-inflammatory, anticancer, neuroprotective, and wound healing activities due to its rich composition of bioactive compounds like triterpenoids, flavonoids, and phenolic acids are also reported (2). One of the primary uses of *Centella asiatica* is in dermatology. The plant's triterpenoids, including asiaticoside and madecassoside, contribute to its potent wound healing properties. These compounds stimulate collagen synthesis, promote cell proliferation, and enhance the tensile strength of newly formed skin. Consequently, *Centella asiatica* is widely used in the treatment of burns, surgical wounds, and hypertrophic scars. Additionally, its anti-inflammatory and antioxidant properties help in managing skin conditions like eczema, psoriasis, and acne, making it a popular ingredient in many cosmetic and pharmaceutical formulations (3). Beyond skin health, *Centella asiatica* is known for its neuroprotective effects. It is used to enhance cognitive function and memory, reduce anxiety, and alleviate stress. The plant's ability to modulate neurotransmitter levels, along with its antioxidant activity, supports brain health and protects against neurodegenerative diseases. Studies have shown that *Centella asiatica* can improve mental clarity, concentration, and overall cognitive performance, making it a valuable herb in managing mental fatigue and age-related cognitive decline (4). Furthermore, it is used in the treatment of leprosy, wound, cancer, fever, allergies, abscesses, asthma, catarrh, convulsions, dysentery, eczema, gonorrhea, hypertension, headache, bronchitis, jaundice, pleuritis, rheumatism, ulcers, spasms,

tuberculosis, urethritis, etc. (5). *Centella asiatica,* applied in the recommended doses, is not toxic and the possible side effects are rare (3). Its diverse therapeutic properties and minimal side effects make it an invaluable component of natural medicine.

Figure 1. *Centella asiatic*a

2. *Centella asiatica* provides a variety of skin healing benefits

2.1. Moisturization and hydration of skin

The skin's stratum corneum layer plays a key role in hydration, housing natural moisturizing factors and a lipid matrix of ceramides, cholesterol, and fatty acids that prevent water loss. Aging skin often experiences diminished hydration and elasticity, leading to common issues like dryness (6,7).

Centella asiatica extract has shown promising results in enhancing skin hydration and barrier function. This botanical ingredient, rich in triterpene saponins, strengthens the epidermal barrier, reducing trans-epidermal water loss and improving skin moisture retention. In clinical trials, creams containing *Centella asiatica* significantly increased hydration and reduced water loss over a four-week period. Additionally, *Centella asiatica* supports collagen synthesis by activating fibroblasts, which is crucial for skin repair and elasticity. Improved blood circulation from its use also enhances nutrient delivery to the skin, supporting its overall health (8,9).

2.2. Anti-acne

Acne develops in areas with sebaceous (oil) glands, particularly on the face and trunk. These glands produce sebum, which can clog hair follicles, leading to Comedones (blackheads or whiteheads). When clogged follicles become a breeding ground for *Propionibacterium acnes,* an inflammatory response occurs, causing redness, swelling, and pustules (10).

Centella asiatica extract contains asiaticoside, a compound that inhibits *P. acnes* growth and has anti-inflammatory properties, reducing acne lesions. Clinical trials have shown that a 5% Centella extract can significantly inhibit acne-causing bacteria (17.3 mm inhibition zone). It also helps heal inflamed acne by promoting tissue repair, balancing sebum production, and reducing redness, making it ideal for acne-prone skin (11,12).

2.3. Sun protection

Centella asiatica plays a crucial role in sun protection as a key ingredient in sunscreen formulations. Ultraviolet exposure is a major contributor to skin damage, leading to conditions like premature aging and increased skin cancer risk. The photoprotective properties of a titrated *Centella asiatica* extract have been shown to mitigate Ultraviolet B-induced damage in human dermal fibroblasts, with studies indicating that this extract restores cell viability and alters microRNA expression in response to ultraviolet exposure (13,14).

The sun protection factor of *Centella asiatica* extract has been measured, revealing increased effectiveness at higher concentrations (15). The therapeutic compound asiaticoside enhances these benefits, improving cell viability and morphology in ultraviolet-exposed cells while inhibiting pathways that contribute to photoaging (16). Asiaticoside, along with another compound, madecassoside,

neutralizes free radicals generated by ultraviolet exposure, reducing oxidative stress and preventing premature aging. They also promote collagen synthesis and improve skin hydration, essential for maintaining skin integrity under sun exposure. Together, these compounds establish *Centella asiatica* as a valuable component in developing effective and multifunctional sunscreens (17,18).

2.4. Anti-aging

Centella asiatica plays a significant role as an anti-aging agent, addressing both chronological aging and photoaging caused by ultraviolet radiation. Photoaging results from oxidative stress, which damages cellular components and accelerates the breakdown of collagen and elastin, essential for skin elasticity and firmness (19). This plant is rich in triterpenoids that enhance skin repair and protect skin cells from ultraviolet-induced damage by improving cell viability and significantly inhibiting lactate dehydrogenase release in HaCaT cells exposed to ultraviolet B irradiation (20).

Centella asiatica also contains castilliferol and castillicetin, which inhibit matrix metalloproteinases (MMPs) enzymes responsible for breaking down collagen and elastin in response to oxidative stress (21,22). By binding to MMPs at active sites, these compounds help reduce collagen degradation. Furthermore, *Centella asiatica* enhances collagen synthesis, maturation, and crosslinking, improving skin structure and reducing wrinkles. Its properties boost microcirculation, aiding in oxygen and nutrient delivery to the skin (23,20). The plant also exhibits antioxidant effects that combat oxidative stress, protecting against premature aging (24).

2.5. Striae

Centella asiatica shows promising effects in managing and preventing striae, commonly known as stretch marks, which result from rapid skin stretching that disrupts the extracellular matrix and damages collagen and elastin fibres. Striae, which frequently appear during pregnancy, puberty, and weight fluctuations, affect a large proportion of women and result in fibrotic skin changes and impaired connective tissue (25-27). *Centella asiatica* aids in striae treatment by promoting fibroblast migration and matrix synthesis, enhancing elastin production, and improving collagen fibre organization and maturation without necessarily increasing collagen quantity (28). This plant's efficacy in reducing striae severity and improving skin health is attributed to its fibroblast-stimulating and elasticity-enhancing properties, making it valuable for striae prevention and management (29,30).

3. Cognitive health and neuroprotection

Mitochondria are essential organelles responsible for producing adenosine triphosphate (ATP) through oxidative phosphorylation, which is crucial for energy metabolism in neurons. CA helps maintain the integrity of the mitochondrial membrane, which is crucial for ATP production. By enhancing mitochondrial function and ATP production, *Centella asiatica* can help meet the high energy demands of neurons, particularly in the context of neurodegeneration where energy deficits are common. *Centella asiatica* also prevents mitochondrial dysfunction and apoptosis which can help preserve neuronal populations that are often lost in neurodegenerative diseases, potentially slowing disease progression and improving cognitive function (31).

It acts as an antioxidant by reducing brain oxidative stress, evidenced by lower malondialdehyde (MDA) levels. It also boosts cholinergic function by lowering acetylcholinesterase (AChE) activity, which enhances the availability of acetylcholine, a key neurotransmitter for memory and learning (32).

Centella asiatica has been found to significantly enhance cognitive abilities in menopausal women.*Centella asiatica* is associated with increased levels of BDNF, a protein crucial for brain health. Higher BDNF levels support neuron survival and promote the growth of new neurons, which is vital for maintaining cognitive function (33).

4. Cardiac and circulatory health

Centella asiatica improves cardiac health through several mechanisms and bioactive compounds, particularly its triterpenes such as asiatic acid, asiaticoside, and madecassoside. Here are the key ways in which it contributes to cardiac health:

4.1. **Antioxidant activity:** C. *asiatica* is rich in antioxidants that help combat oxidative stress in cardiac tissues. By neutralizing free radicals, it protects heart cells from oxidative damage, which is crucial for maintaining overall cardiac function.
4.2. **Anti-inflammatory effects:** The plant exhibits significant anti-inflammatory properties, which help reduce inflammation in the cardiovascular system. Chronic inflammation is a key factor in the development of various heart diseases.
4.3. **Improvement of lipid profiles:** C. *asiatica* has been shown to lower cholesterol levels and improve lipid metabolism. By reducing levels of LDL (bad cholesterol) and increasing HDL (good cholesterol), it helps prevent atherosclerosis and other cardiovascular conditions.
4.4. **Enhancement of endothelial function:** The extracts of C. *asiatica* improve endothelial function, which is essential for regulating blood flow and maintaining vascular health. Healthy endothelial function helps prevent hypertension and reduces the risk of cardiovascular events.
4.5. **Regulation of blood sugar levels:** The antidiabetic properties of C. *asiatica* help manage blood glucose levels, which is important for preventing diabetes-related cardiovascular complications. By controlling hyperglycemia, it supports overall cardiac health (31-33).

5. Digestive health

Centella asiatica augments digestive health through antioxidant, anti-inflammatory, and prebiotic properties, promoting beneficial gut bacteria and suppressing pathogens (34,35). This is particularly valuable for conditions like Small Intestinal Bacterial Overgrowth and Inflammatory Bowel Disease. Polyphenols in *Centella* balance gut microbiota, and decoction-based preparations boost polysaccharides, enhancing prebiotic effects (34). As a Rasayana, it rejuvenates digestive function, while nervine tonic effects alleviate stress-related digestive issues (35). Key compounds like Asiatic and madecassic acids provide anti-inflammatory and healing benefits, supporting conditions such as gastritis, ulcers, and liver-related digestive disorders (36,37).

6. Wound healing, anti-inflammatory and antioxidant property

Centella asiatica has been used for wound healing due to compounds like asiatic acid and madecassic acid, which promote fibroblast proliferation, collagen synthesis, and angiogenesis, improving blood flow and tissue regeneration. Asiaticoside enhances wound contraction and re-epithelialization, accelerating healing and reducing oxidative stress (38,39). Its anti-inflammatory properties reduce cytokines and inhibit COX-2, helping soothe sensitive skin and chronic inflammation. Antioxidant and antimicrobial qualities make it valuable in cosmetics for calming acne, eczema, and promoting youthful skin (40,41). *Centella asiatica,* a herb known for its medicinal properties, is renowned for its antioxidant activity due to its rich content of phenolic compounds, flavonoids, and triterpenoids. Phenolic compounds like chlorogenic acid, catechin, and quercetin are abundant in *Centella asiatica* and are known for scavenging free radicals and reducing lipid peroxidation, thus protecting cellular components from damage (42). The extracts, containing gluconic acid, ferulic acid, kaempferol, chlorogenic acid, and asiatic acid, provide excellent antioxidant and anti-hyperlipidemic properties, potentially useful for treating diseases like hyperlipidemia (43). Asiaticoside, a triterpene, enhances key antioxidant enzymes such as superoxide dismutase (SOD), reduced glutathione (GSH), and vitamin E, bolstering the skin's natural defenses (44). The antioxidant mechanisms include preventing chain initiation, binding metal ions, decomposing peroxides, and scavenging radicals (45). Several studies support the antioxidant efficacy of *Centella asiatica*. For example, an in vitro study showed strong DPPH radical scavenging activity (46). In vivo studies demonstrated that treatment with *Centella asiatica* reduced renal and brain levels of pro-inflammatory cytokines (MDA, TNF-α, IFN-γ) and increased anti-inflammatory cytokines (IL-4, IL-10), along with significantly boosting antioxidant status (47).

7. Conclusion

Centella asiatica offers a versatile natural remedy, positively impacting skin repair, neuroprotection, cardiovascular function, and digestion through its antioxidant and anti-inflammatory actions. Clinical and traditional applications substantiate its effectiveness in promoting skin elasticity, cognitive function, cardiac health, and wound healing. Its minimal toxicity and rich composition support its role in therapeutic and cosmetic formulations, making *Centella asiatica* a promising herb in modern healthcare and wellness products in India.

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Empowering wellness through phytopharmaceuticals:Antioxidants and their role in lifestyle disease prevention



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Abstract

Phytopharmaceuticals hold immense potential for India, especially as many natural products and plant-derived compounds are already integrated into daily diets through foods like vegetables, fruits, and herbs. Common dietary items such as turmeric, ginger, and garlic, as well as leafy greens, pulses, and spices, are not only rich in nutrients but also possess antioxidant properties that contribute to overall wellness and disease prevention. Although many people use these natural products regularly, there is still a lack of awareness, and many misunderstand their real health benefits and healing power. Phytopharmaceuticals have demonstrated effectiveness in reducing the risk of certain diseases by combating oxidative stress and supporting immune health. There is a need for greater public awareness on the effective and scientifically-backed use of phytopharmaceuticals, which could serve as preventive healthcare measures in reducing lifestyle-related diseases. By addressing myths and encouraging informed consumption, India can leverage its rich biodiversity and traditional knowledge to enhance public health outcomes and foster a sustainable approach to wellness.

Keywords: Phytopharmaceuticals, Antioxidant, Disease, Benefits, Healthcare

1.Introduction

Phytopharmaceuticals, derived from plants, play a crucial role in promoting health and preventing diseases (1). The increasing awareness of their antioxidant properties has led many people to incorporate various fruits and vegetables into their daily diets (2). Antioxidants are substances that help prevent or delay the oxidation process in our bodies, which can cause cell damage and contribute to chronic diseases (1-3). Common sources of antioxidants include fruits like berries, vegetables such as spinach and lettuce, and herbs like turmeric and ginger (2). Research indicates that only a small percentage of the population understands the appropriate quantities of fruits and vegetables to consume daily. For optimal health, adults are generally advised to include at least 400 grams of fruits and vegetables in their meals each day. This can be achieved by consuming a variety of colorful foods, as each color often represents different beneficial compounds (3,4).

Timing also plays a significant role in maximizing the health benefits of these foods (2). Consuming fruits and vegetables at specific times, such as having a fruit smoothie in the morning or a salad with lunch, can enhance their antioxidant effects and improve overall well-being. For instance, eating vegetables during lunch can help in digestion, while having fruits as snacks can satisfy cravings and provide essential nutrients (5,6). Currently, there is a pressing need to educate the public about the importance

of phytopharmaceuticals. By increasing awareness, we can empower individuals to make healthier choices that may reduce the risk of lifestyle diseases such as diabetes, heart disease, and certain types of cancer (7,8). Initiatives aimed at promoting the consumption of fruits and vegetables, along with understanding their antioxidant properties, will be key to improving public health outcomes in India (2).

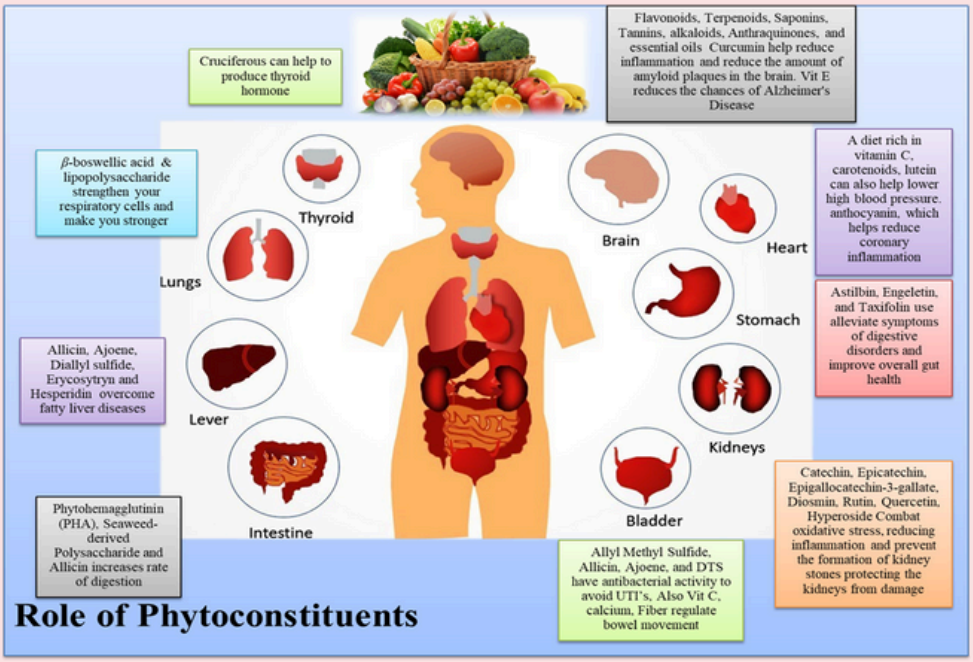

Figure 1. Role of Phytoconstituent

2. Phytoconstituents

Phytoconstituents from natural sources like vegetables, fruits, spices, and herbs provide potent antioxidant effects that can help prevent lifestyle diseases. Here are key phytoconstituents, with recommendations for age-appropriate intake, health benefits, and consumption patterns (8).

2.1. Curcumin

Curcumin is found primarily in turmeric, offers significant anti-inflammatory and antioxidant effects, supporting liver, joint, and heart health by neutralizing free radicals and inhibiting inflammatory enzymes (9). The European Food Safety Authority says that the safe daily amount of curcumin is between 0 and 3 mg for every kilogram of body weight. This is about 0 to 1.4 mg for each pound of body weight. To meet this requirement, children should consume 1/4 teaspoon daily, adults should have 1/2 teaspoon, and the elderly can take up to 1 teaspoon, along with black pepper to improve absorption (10,11).

2.2. Quercetin

Quercetin is present in apples, onions, and berries, has powerful antioxidant and anti-inflammatory properties that protect cells from oxidative stress, improve heart health, and reduce allergy symptoms by stabilizing histamine-releasing cells (12). Quercetin, the most common flavonoid in the diet, is typically consumed in amounts of 10–100 mg per day from foods like onions, apples, grapes, berries, broccoli, citrus fruits, cherries, green tea, coffee, red wine, and capers. Children can achieve this by eating a quarter of an apple or a small handful of berries, while adults and seniors can benefit from one whole apple or a small serving of berries. For best results, consume these fruits fresh (13).

2.3. Resveratrol

Resveratrol is found in grapes, blueberries, and peanuts, supports cardiovascular and brain health by reducing oxidative stress and activating enzymes linked to longevity (11). Clinical trials indicate that resveratrol is generally safe at doses up to 1g. However, consuming more than 2.5g per day may cause abdominal issues, including cramps, gas, and nausea. Children can get this benefit from 3-4 grapes or a few blueberries, while adults can have a small bowl and seniors the same portion. For optimal results, it's best to consume these fresh (13).

2.4. Catechins

Catechins are abundant in tea, green tea, enhance metabolism and heart health by scavenging free radicals and reducing LDL cholesterol oxidation (14,15). The average daily intake of catechins was 50 mg. As age increased, so did catechin consumption, with women having a higher intake (60 mg/day) compared to men (40 mg/day). Tea served as the primary source of catechins across all age groups. Green tea is good for older children and adults. Adults can have 1-2 cups daily, and seniors should have one cup. It works best when steeped in hot (not boiling) water, and adding lemon juice can increase its benefits (13,14,16).

2.5. Lycopene

Lycopene is present in tomatoes and watermelon, reduces cancer risks and supports heart health, particularly by protecting skin and prostate cells and DNA from oxidative damage (17,18). The recommended daily intake of lycopene is up to 30 mg, which is considered safe. For children, this can be achieved by consuming 1/4 cup of tomato-based foods, while adults and seniors should aim for 1/2 cup. Cooking these foods helps enhance the bioavailability of lycopene (14,17).

2.6. Vitamin C

Vitamin C from citrus fruits and bell peppers, supports immunity, collagen production, and iron absorption while protecting skin health (16). Children can have half an orange or a quarter of a bell pepper. Adults and seniors can also benefit from one medium orange or half a cup of bell peppers each day, preferably eaten fresh to maximize their nutritional value. This portion provides the average recommended daily intake of 50 mg (19).

2.7. Beta-carotene

Beta carotene is found in carrots and sweet potatoes, converts to vitamin A in the body, benefiting vision, immunity, and skin health (20). Recommended servings are a few carrot sticks for children and 1/2 cup for adults and seniors, providing 12-16mg per day. It's best to have them lightly steamed or roasted to improve absorption (21).

2.8. Anthocyanins

Anythocyanins are abundant in berries, provide anti-inflammatory and brain-health benefits by neutralizing harmful oxidants, potentially reducing cognitive decline. A small portion of berries each day is appropriate for all age groups and is most beneficial when consumed fresh. This will meet the daily intake of ACNs is estimated to be 12.5 mg/day/person (22-24).

2.9. Allicin

Allicin is present in garlic, offers antibacterial properties and supports cardiovascular health by reducing blood pressure and cholesterol levels (25,26). Small children may avoid it because of its strong taste, but older children, adults, and seniors can have one clove daily, while seniors can take 1-2 cloves. This provides the needed 0.1mg daily dose, preferably eaten raw, as cooking lowers its allicin content (27,28). Finally, flavonoids in citrus fruits, apples, and onions promote heart health by reducing inflammation and oxidative stress. Children can consume a quarter of an orange or a few apple slices, while adults and seniors should have one orange or apple daily. This food will accomplish 10-15mg daily dose (29-31).

Table 1. List of Phytoconstituent, Source, dose and mode of action (9-31)

Phytoconstituent	Sources	Daily Dose	Mechanism of Action
Curcumin	Turmeric	Children: 1/4 tsp; Adults: 1/2 tsp; Seniors: 1 tsp (with black pepper)	Neutralizes free radicals; inhibits inflammatory enzymes, supporting liver and joint health

Quercetin	Apples,Onions, Berries	Children: 1/4 apple or few berries; Adults & Seniors: 1 apple or small berry serving	Stabilizes histamine cells, reducing oxidative stress and inflammation; supports heart health
Resveratrol	Grapes, Blueberries, Peanuts	Children:3-4 grapes or a few blueberries; Adults & Seniors: small bowl	Activates longevity enzymes, reduces oxidative stress; supports cardiovascular and brain health
Catechins	Green tea	Teens & Adults: 1-2 cups; Seniors: 1 cup	Scavenges free radicals, reduces LDL oxidation, supporting heart and metabolic health
Lycopene	Tomatoes, Watermelon	Children: 1/4 cup; Adults & Seniors: 1/2 cup (cooked for better absorption)	Neutralizes free radicals; protects skin and prostate cells, reducing cancer risks
Vitamin C	Citrus fruits, Bell peppers	Children: 1/2 orange or 1/4 bell pepper; Adults & Seniors: 1 orange or 1/2 bell pepper	Boosts immune function and collagen production; enhances iron absorption and skin health
Beta-Carotene	Carrots, Sweet potatoes	Children: few carrot sticks; Adults & Seniors: 1/2 cup (steamed or roasted)	Converts to vitamin A, supporting vision, skin, and immune health; neutralizes free radicals
Anthocyanins	Berries (e.g., Blueberries)	All ages: Small handful	Reduces inflammation, supports brain function, protects cells from oxidative damage
Allicin	Garlic	Older children, Adults & Seniors: 1-2 cloves (raw preferred)	Reduces blood pressure and cholesterol; prevents platelet aggregation, supporting heart health
Flavonoids	Citrus fruits, Apples, Onions	Children: 1/4 orange or few apple slices; Adults & Seniors: 1 orange or apple	

3. Marketed preparation

For those who find it difficult to meet their daily nutritional needs through food alone, various marketed supplements can help fulfill the requirements for essential phytoconstituents like curcumin, quercetin, and resveratrol (27). These supplements are available in several forms, including tablets, capsules, powders, and soft gels, making them easy to incorporate into daily routines. For example, curcumin supplements, often combined with black pepper extract (piperine) to improve absorption, are available as capsules or tablets and are typically taken orally once or twice a day (26). Quercetin supplements, often combined with vitamin C to enhance effectiveness, are available in tablet or capsule form and are usually taken with meals to improve absorption. Similarly, resveratrol supplements, available in capsule form, are often recommended as a daily dose to support heart and brain health. By choosing these convenient supplement forms, individuals can more easily meet their daily intake of key antioxidants and support their overall health, even on days when a balanced diet is challenging (31).

4. Conclusion

Phytopharmaceuticals are powerful natural remedies that help prevent lifestyle diseases with their strong antioxidant and anti-inflammatory effects. Foods like turmeric, berries, and green tea contain

these beneficial compounds, supporting heart, brain, and immune health. For those who cannot meet their daily nutritional needs through food alone, supplements in forms like capsules and powders can be a helpful option. By spreading awareness about these plant-based nutrients, people in India can make informed choices that improve their health and wellness.

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Phytopharmaceuticals in skincare: A new frontier in natural beauty

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Abstract
The cosmetics business is progressively adopting natural and plant-based components, with phytopharmaceuticals at the forefront. Phytopharmaceuticals are derived from medicinal plants and are known for their bioactive components, which provide several advantages to the skin. Antioxidant, anti-inflammatory, antibacterial, and moisturizing characteristics help to reduce aging signs, soothe irritation, prevent acne, and improve skin suppleness. With India's abundant botanical resources and growing consumer preference for natural goods, phytopharmaceuticals have great growth potential in both domestic and international skincare markets. This article highlights the potential for the growth of phytopharmaceuticals in India.

Keywords: Phytopharmaceuticals, Skincare, Bio-active compound

1. Introduction

Preparations of natural ingredients have been traditionally used for centuries for skin care purposes; nowadays they are becoming more popular in modern formulations due to consumers' concerns about synthetic ingredients/chemical substances. Growing consumer awareness and the need for safer, more sustainable goods have caused a major shift in the beauty and skincare business in recent years, favouring natural and plant-based components. Phytopharmaceuticals, or bioactive substances produced from therapeutic plants, are at the vanguard of this movement. The skincare sector has shown a strong interest in phytopharmaceuticals as a means of achieving natural beauty. Chemicals and synthetic ingredients, used in many skincare and cosmetic products, can cause a variety of undesirable side effects, especially for people with sensitive skin and potential allergic reactions. The overwhelming array of synthetic and potentially harmful ingredients used in skincare and cosmetic products (health hazards associated phthalates, parabens, petroleum-based chemicals, aluminium salts, etc.) are main reason for freshly produced organic and natural skincare, based on innovative and up to date multifunctional and effective formulations which include products with anti-aging, skin lightening and super moisturizing benefits (1).

1.1. What are phytopharmaceuticals ?

A phytopharmaceutical drug is defined as a purified and standardized fraction with a defined minimum of four bio-active or phytochemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation, or prevention of any disease or disorder but does not include administration by parenteral route (2).

1.2. Is there any potential for phytopharmaceuticals in India?

The massive expansion of the manufacturing and digital industries has raised demand for skin care products in India, making it one of the fastest-growing categories in the personal care category, with more enterprises attempting to address consumers' specific demands. The India Skin Care Market was predicted to be valued 2.56 billion USD (United States Dollar) in FY2023 (3).

As more individuals in India began to feel that healthy skin not only promotes physical well-being but also helps to retain beauty, the skincare market expanded dramatically. Customers want to focus on healthy skin, whether that means following a basic skincare program or experimenting with products manufactured with specific ingredients.

Herbal treatments are widely regarded as a viable alternative to current allopathic therapy. Since time immemorial, humans have employed herbal medicines to address a variety of healthcare requirements. Approximately 80% of the population in underdeveloped countries use herbal remedies to treat a variety of ailments. India is a major producer of medicinal herbs and is known as the world's botanical garden. There are unmet medical needs for the research and development of phytopharmaceuticals. Although herbal remedies are widely used in society, only a few medicinal herbs have been properly examined for their efficacy in medical treatments (4).

2. Phytopharmaceuticals in skincare

Phytopharmaceuticals in skincare offer a range of benefits due to their natural origin and bioactive compounds. They are used for their antioxidant, anti-inflammatory, anti-microbial, hydrating, skin brightening properties. Natural sunscreens, such as those derived from green tea, provide UV protection. Additionally, phytopharmaceuticals can enhance collagen production, promoting skin firmness and reducing wrinkles

2.1. Antioxidant properties

Plant extracts contain antioxidants such as vitamins, flavonoids, and polyphenols. These substances protect the skin from free radical-induced oxidative stress, which can result in premature aging and skin damage. Antioxidants help to neutralize free radicals, which prevents cellular damage and promotes skin vitality (5).

2.2. Anti-inflammatory effects

Many phytopharmaceuticals have powerful anti-inflammatory qualities, which help to soothe sensitive skin and reduce redness. Green tea extract and aloe-vera are typical ingredients used in formulations to soothe the skin and treat inflammatory diseases such acne and eczema (5).

2.3. Anti-microbial activity

Plant extracts with antimicrobial characteristics can treat bacterial, fungal, and viral skin problems. Tea tree oil and neem extract, for example, are effective against acne-causing germs, resulting in clearer and healthier skin (5).

2.4. Skin barrier enhancement

Phytopharmaceuticals can improve skin barrier function, which helps maintain moisture and defend against external aggressors. Plant-derived ingredients such as ceramides serve to improve the skin's natural barrier, decreasing trans-epidermal water loss and increasing hydration (5).

2.5. Skin whitening

In recent years, researchers have concentrated on anti-tyrosinase medicines due to their ability to whiten skin and treat pigmentation problems. Current research indicates that numerous plant extracts and related substances are excellent tyrosinase inhibitors, lowering melanin overproduction in the epidermis. Importantly, these drugs block melanogenesis without cytotoxic or mutagenic effects on melanocytes (6,7).

2.6. Moisturizer

Natural substances like coconut oil, sunflower oil, and aloe vera offer significant skin moisturizing benefits. Coconut oil effectively hydrates and softens the skin, while sunflower oil, rich in lecithin and tocopherols, provides smoothing properties without clogging pores. Aloe vera is known for its soothing and nourishing qualities, making it a popular cosmetic ingredient (8).

Table 1. Contents highlighting plant-derived actives and their benefits

Name	Plant Active	Activity	Ref
Gingko (*Gingko Biloba)*	Flavonoids	Prevent UVB-induced photoaging, anti-inflammatory, antioxidant, and blood microcirculation	(9)
Turmeric (*Curcuma Longa)*	Phenolic compounds	Anti-inflammatory,antioxidant, treatment of psoriasis	(10)
Chest nut	Polyphenols	Moisturizer, in the treatment of oxidative stress-mediated diseases and photoaging	(11,12)
Green tea (*Camellia sinensis)*	Flavanoids,Catechins	Antioxidant (20 times stronger than vit E); ability to heal UV photo-damage and phototoxicity; stimulates the formation of ceramides	(12,13)
Aloe vera *(Aloe barbadensis)*	Polysaccharides, saponins, anthraquinones	Soothing and cooling effect; antimicrobial, antifungal, wound healing and anti-inflammatory	(14,15)
Ginger (*Zingiber Officinale)*	Gingerols and shogaol	Antioxidant effect nearly equal to that of synthetic antioxidants, including BHA and BHT, prevents free radical generation and reduces OxS;Antibacterial and anti-fungal Activity	(16,17,18)
Licorice *(Glycyrrhiza glabra)*	Glycoside glycyrrhizin, glycyrrhetinic acid, flavonoids, isoflavonoid	Skin whitening,Antioxidant,Antimicrobial, And anti-inflammatory	(19,20)

3. Challenges faced

Herbal medications have been used for thousands of years because they are natural, have fewer side effects, and are effective. Despite their long history and widespread use, the development and promotion of herbal medications face significant hurdles.

3.1. Formulation development

Integrating herbal medicine into skincare products necessitates rigorous research approaches that integrate ancient practices with current medical standards (21).

3.2. Stability of herbal skincare products

Herbal skincare products suffer stability issues due to their chemical complexity and natural enzyme activity, necessitating extensive stability testing to ensure quality and safety (21).

3.3. Pharmacokinetic information

Limited pharmacokinetic data makes it difficult to determine optimal dosages for herbal skincare products, resulting in unpredictable therapeutic outcomes (21).

3.4. Regulation and efficacy

The regulatory frameworks for herbal skincare products vary, influencing their classification and distribution. Ensuring safety, efficacy, and quality is critical (21).

3.5. Quality assurance and control

Establishing quality standards and Good Manufacturing Practices (GMPs) is critical for herbal skincare. Inconsistent practices might cause variances in product quality (21).

3.6. Obstacles for clinical trials

Clinical studies for herbal skincare products require guaranteeing homogeneity of active components and adequate trial techniques in order to get reliable clinical data (21).

3.7. Regulatory and ethical considerations

Herbal skincare research must manage regulatory and ethical hurdles, such as patient participation and placebo effects, while adhering to WHO clinical trial criteria (21).

To summarize, while herbal skincare products have considerable potential, their development needs overcoming hurdles in formulation, stability, pharmacokinetics, regulation, quality control, and clinical trials to ensure consistent efficacy and safety.

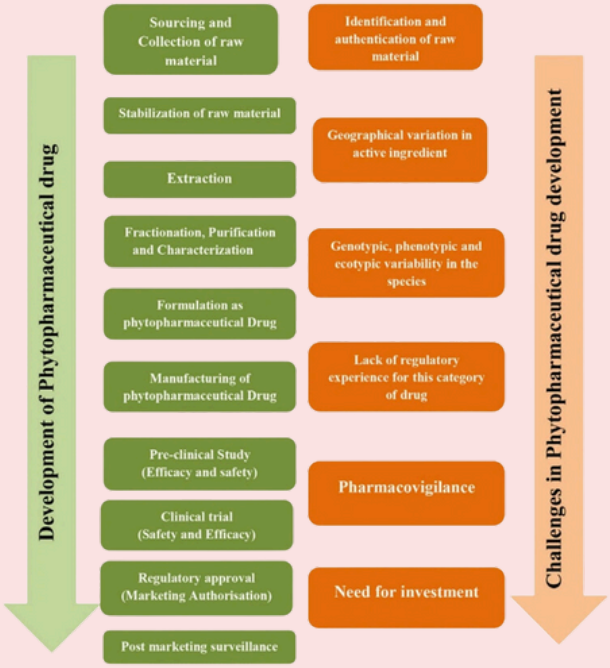

Figure 1. Steps involved in the development of phytopharmaceutical drug and its challenges

4. Scope

Phytopharmaceuticals are in high demand for medical and nutritional purposes, which presents several potential. India's biodiversity enables the production and export of therapeutic plants, which benefits the economy. Increased demand in the herbal business opens up clinical and research opportunities, as many herbs' therapeutic potential has yet to be fully understood. The three major Indian traditional medicinal systems (Ayurveda, Unani, and Siddha) generate approximately $500 million in annual revenue. Furthermore, the herbal business generates jobs for farmers, villagers, industrial workers, and researchers, promoting innovation and economic progress (22).

The estimated market for herbal medicines by 2023 was $111billion, which may become an impressive market for phytopharmaceuticals due to the availability and confidence of scientific evidence, outclassing the herbal and allopathic sector market. In India, 90% of herbal medication raw materials are obtained from natural sources with diverse geographical distribution. Accurate identification and quality assurance of the starting material are necessary. The scope for phytopharmaceuticals in skincare is significant because natural ingredients are increasingly preferred for their effectiveness and fewer side effects compared to synthetic chemicals. India's rich botanical resources, combined with traditional knowledge, provide a robust foundation for developing high-quality skincare products. This positions India as a leader in the global skincare market, leveraging its natural resources and traditional expertise to meet growing consumer demand for safe and effective skincare solutions (22).

5. Conclusion

Phytopharmaceuticals are more advantageous in skincare than generic chemicals since they provide natural, effective, and safer alternatives. Plant-based compounds frequently have fewer adverse effects and offer extra therapeutic benefits such as anti-inflammatory, antioxidant, and antibacterial activity. These benefits address the growing customer demand for natural and holistic skincare products. India's abundant botanical resources and traditional expertise make it particularly positioned to develop and innovate in this industry, satisfying the growing worldwide need for safe and effective skincare products. This strategic focus on phytopharmaceuticals has the potential to drive tremendous development and innovation, cementing India's position as a worldwide skincare leader.

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Botanical allies: Phytoconstituents in hepatoprotection

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Abstract

The liver's functions are essential for maintaining overall human health. With the rising global incidence of liver diseases, especially viral hepatitis which resulted in 1.3 million deaths in 2022 it's important to implement effective testing, treatment, and prevention strategies. In many developing countries, herbal medicine has gained prominence as an alternative to allopathic treatments, with around 80% of the population relying on traditional remedies for health concerns. India, often referred to as the "botanical garden of the world," boasts a rich heritage of using hepatoprotective herbs, including turmeric and milk thistle, to support liver health, with identification of over hundred plants with hepatoprotective phytoconstituents. While modern medicine has made strides in treating liver diseases, herbal remedies present a viable alternative, often with fewer side effects and better safety profiles. This review highlights the significance of integrating traditional herbal knowledge into contemporary medical practices for enhancing liver health and managing liver diseases effectively; emphasizing on understanding the mechanism and factors affecting hepatotoxicity, different phytoconstituents used as hepatoprotectives, their proposed mechanism of action and recent studies.

Keywords: Hepatoprotection, Hepatotoxicity, Hepatitis, Phytoconstitutents, Antioxidants

1. Introduction

Liver's functions are vital for maintaining overall health and homeostasis in the body. A liver performs over 500 vital functions every single day to keep us alive (1). It produces bile, which is essential for digestion and absorption of fats in the intestine; stores vital nutrients, including vitamins, minerals, and glycogen; synthesizes important proteins, such as clotting factors and albumin. That's why testing, treating and preventing liver diseases is so important.

According to WHO statistics, deaths associated with viral hepatitis are on the rise. In 2022, hepatitis B and C together led to 1.3 million fatalities. Approximately 304 million individuals are currently living with a chronic viral hepatitis infection. Each day, around 3,500 people lose their lives due to hepatitis B and C, which translates to one death every 30 seconds. Additionally, over 6,000 new viral hepatitis infections occur daily (1).

Globally, herbal medicine is recognized as a prominent alternative to modern allopathic treatments. In fact, around 80% of people in developing countries depend on herbal remedies to tackle various health concerns. India is notable for being one of the biggest producers of medicinal plants, known as the "botanical garden of the world." Herbs are used for preventive and therapeutic action since long time. Recently, there has been significant research on use of Indian traditional herbs to enhance hepatic function and address liver diseases (2).

1.1. Brief history

Hepatoprotective herbs have been utilized in traditional medicine for centuries, showcasing various cultures' understanding of liver health. Ancient Egyptians recognized herbs like coriander and fenugreek, while traditional Chinese medicine has used milk thistle (*Silybum marianum*) and dandelion (Taraxacum) for over 2,000 years. Ayurveda in India employs turmeric (*Curcuma longa*) and triphala for liver support. In medieval Europe, artichoke (*Cynara scolymus*) and chicory (*Cichorium intybus*) were valued for liver function. The Renaissance revived herbal knowledge, leading to scientific interest in the 20th century, with studies validating anti-inflamatory and antioxidant properties of milk thistle. Today, these herbs are recognized in dietary supplements for managing liver diseases, with ongoing research supporting their integration into modern medicine. In a report around hundred with fifty eight phyto-compounds have been categorized based on their chemical classification contributing to hepatoprotective activity (3).

2. What is hepatotoxicity?

Liver in human body receives dual blood supply, hepatic artery contributing approximately twenty percent of blood and portal circulation contributes remaining eighty percent. Twenty to twenty five percent of the total cardiac output is to the liver indicating importance of liver's functions. Mentioning the most important function, liver filter toxic substances, including many medications like chemotherapeutic drugs such as antibiotics, acetaminophen etc. In general, when human body is exposed to xenobiotics, site-specific microbiomes present in or associated with gastrointestinal tract, respiratory tract and skin are primarily exposed. This microbiome mediates first pass hepatic metabolism before their absorption to other organ systems (4). Amongst these systems of entry, most interactions occur in human gut, in presence of gut microbiota that includes bacteria, fungi, archaea, and viruses. Liver metabolizes drugs via different type of reactions converting toxins into water soluble conjugated substances via P450 enzymes and these soluble substances are excreted. Any disturbance in these metabolic processes may cause hepatotoxicity. Hepatotoxicity refers to liver damage caused by exposure to xenobiotics, including drugs, alcohol, environmental toxins, and even some dietary supplements.

Hepatotoxicity may happen through various mechanisms. It includes direct cellular injury by certain drugs or toxins, oxidative stress leading to dismantle, detachment and programmed cell death of hepatocytes, bile duct injury, mitochondrial inhibition and activation of cytotoxic T-cells. In some cases, liver metabolizes substances to reactive intermediates whose toxicity is more than parent compound. Hepatotoxicity due to paracetamol is an example where highly reactive metabolite binds to cellular macromolecules leading to injury. Further, some compounds cause hepatic injury due to accumulation of acids resulting from interference with bile formation and flow. Hepatic toxicity may initiate inflammatory response, resulting in activation of immune reactions and release of pro-inflammatory cytokines.

3. Hepatoprotection

Liver serves many interrelate functions of human body. Hence, knowledge and management of hepatic diseases is very important. Hepatoprotection refers to practices followed for prevention of hepatic damage and promotion of liver health. This includes modification in lifestyle and dietary choices; use of supplements and medicines that support liver functions. Progress in allopathic medicine for management of hepatic disease has been witnessed since last many years. Commonly used approaches include use of corticosteroids and interferons (5), Lamivudine for treatment of hepatitis B and cirrhosis, propylthiouracil for alcoholic hepatic diseases, ursodeoxycholic acid and rosiglitazone for non-alcoholic fatty hepatic disease. It has been observed that treatment with corticosteroids and interferons is inconsistent with evident side effects and is not cost effective, regular dose of lamivudine may result in a resistant hepatitis B virus mutant (6) arrival, treatment with propylthiouracil renders metabolically compromised patients hypothyroid (7), rosiglitazone increases risk of heart attack (8).

Thus, use of alternative system of medicine, particularly use of herbs, has been promoted. World Health Organization (WHO) has said 'the traditional medicine especially herbs as therapeutic

practices have been emerged for hundreds of years, before the development of modern medicine and are still in use today.' Herbs are used for hepatoprotection and for treatment of hepatic disorders as well since long. This has also been reported that inspite of prevalence of modern medicine, drugs stimulating hepatic function, hepatoprotection, stimulating regeneration of hepatic cells are very less (9). Some of phytoconstituents, especially polysaccharides, proteins and flavanoids, lignans, rotenoids, etc., has potential to modulate the immune system. There are many hepatoprotective and immunomodulatory herbs reported in literature, owing to lesser cost, lesser undesirable drug reactions and better safety profile.

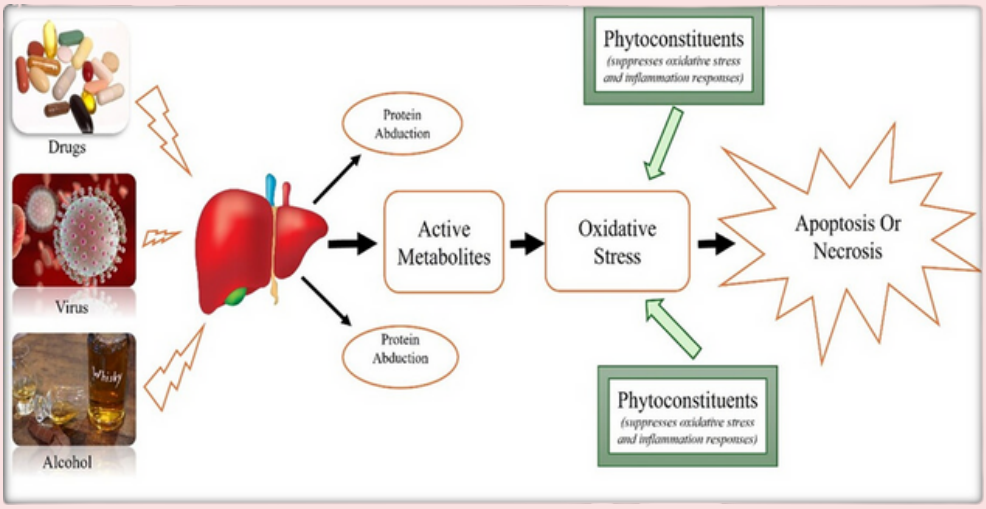

Figure 1. Mechanism of hepatotoxicity and hepatoprotection

Various proposed mechanism of hepatoprotection using phytoconstituents are reduced peroxidation, activation of anti-inflammatory response, inhibition of collagen deposition and antifibrotic effect, free radical scavenging and antioxidant activity. Fig 1 depicts general mechanism of induction of hepatotoxicity and hepatoprotection. Here are some notable phytopharmaceuticals that have been studied for their hepatoprotective properties:

3.1. Silymarin, silibinin, silybin and silydianin (Flavanolignans)

These flavonolignans are isolated from the species Silybum marianum. Common Name of species is Milk thistle. This herb is effective in alcohol, viral and drug induced hepatic diseases (10). Silymarin stabilizes biological membrane and enhances protein synthesis, owing to its anti-inflammatory, antioxidant and anti-fibrotic activities. It shows its antioxidant activity by enhancing hepatic glutathione and thus enhancing the ability to inhibit free radical production, damage caused to cellular membranes and lipoperoxidation. Further, it shows enhanced protein synthesis in hepatocytes by stimulating RNA polymerase I activity (11-14). This plant contains Silymarin, silybin A, silybin B, isosilybin A, isosilybin B, silychristin A, silychristin B, and silydianin and one flavonoid taxifolin.

3.2.Resveratrol

Resveratrol is a type of polyphenol, hydroxylated derivative of stilbene (3,5,4′-trihydroxy-*trans*-stilbene). It is a phytoalexin that is obtained by many plants as defensive response to attack by pathogens or injury (15). It occurs in the skin of fruits like grapes, blueberries, raspberries, mulberries (16,17). The proposed mechanism of action of resveratrol is its influence on the metabolic pathways affecting cellular development; metabolic pathways controlling cell differentiation, growth, and proliferation and metabolic pathways regulating immune responses and cellular reactions. Further, it has been reported to improvise glucose metabolism, lipid profile and lessens hepatic fibrosis. It has potential to treat hepatic diseases induced by non-alcoholic fatty liver disease (NAFLD) (18).

3.3.Corilagin, isocorilagin, kaempferol rhamnoside, and brevifolin carboxylic acid

These are polyphenolic constituents obtained from extract of *Phyllanthus niruri*. This is one of most common species of genus *Phyllanthus*, family Phyllanthaceae. It is widely distributed plant. Known with different names in different regions of worls, namely, "punarnava" in India,"dukunganak"

in Malaysia, “chanca piedra” in Spain, “quebra pedra” in Brazil and “praparai mi” in Paraguay. In addition of polyphenolic compounds, its parts (root, stem and leaf) contain other biological constituents like lignans, flavonoids, glycosides, alkaloids, sterols, lipids, and phenylpropanoids that possess beneficial effects on human health.

Aqueous extract of *Phyllanthus niruri* has been reported to contain corilagin, isocorilagin, brevifolin, quercetin, kaempferol rhamnoside, gallic acid, and brevifolin carboxylic acid. Amongst these, corilagin, isocorilagin, kaempferol rhamnoside and brevifolin carboxylic acid exhibits highest hepatoprotective activity, attributed to its antioxidant effects; with moderate activity owned by other phytoconstituents. The aquesous extract has been reported to normalize levels of hepatic enzymes, total cholesterol, triglycyrides, total bilirubin, glucose, total proteins, urea and creatinine levels that are elevated in xenobiotic induced hepatotoxicity. Proposed mechanism of action is it antagonizes the effect of toxins on antioxidant enzymes superoxide dimutase, catalase, glutathione reductase, and glutathione peroxidase; thus reduces lipid peroxidation (19). More examples of hepatoprotective herbal phytoconstituents is listed in Table 1:

Table 1. Common hepatoprotective herbs

Plant	Phytoconstituent	Proposed Mechanism of Action	Ref.
Curcuma longa Family:Zingiberaceae Common Name: Turmeric	Flavonoid: curcumin (diferuloylmethane)Volatile oils: tumerone, atlantone, and zingiberone	It inhibits the formation of pro-inflammatory cytokines, thus enhancing the protection against oxidative damage to hepatocytes. Additionally, it reverses biliary hyperplasia, fatty changes in liver.	(20)
Taraxacum officinale Family:Taraxacum officinale Common Name: Dandelion	Phenolics, flavonoids, tannins, polysaccharides and ascorbic acids.Flavonoid glycosides include luteolin 7-glucoside, luteolin 7-diglucosides; coumarins,cichoriin, aesculin; Sesquiterpenoid phytoalexin includes Lettucenin A, 4-hydroxyphenylacetate inositol esters, aesculin, caffeic acid, chlorogenic acids, apigenin, isovitexin, chicoric acid; Polyphenols includes hydroxycinnamic acid derivatives and flavonoid glycosides.	Antioxidant activity is exhibited by strengthening activity of catalase, glutathione peroxidase, glutathione-S-transferase, glutathione reductase and glutathione.Strengthening of enzymes results in less of reduction of lipid peroxidation and more of antioxidant activity.	(21- 25)
Morinda citrifolia Family: Rubiaceae Common Name: Noni	Ehydromethoxygaertheroside, dehydroepoxymethoxygaertheroside, borreiagenin, citrifoside, pheophorbide A, pyropheophorbide A, ursolic acid, and flavanoids	It enhances activity of hepatic enzymes superoxide dismutase and glutathione peroxidase. Thus, lessens infiltration of lipids, preventing mitochondrial damage, and maintains overall liver health.	(26)
Andrographis paniculata Family:Acanthaceae Common Name: green chiretta	Diterpenoids including neoandrographolide, andrographolide, dehydroandrographolide), Phenolic compounds includes caffeic acid, chlorogenic acid, and protocatechuic acid; xanthones (1,8-dihydroxy-3,7-dimethoxyxanthone1,8-dihydroxy-3,7-dimethoxyxanthone) and flavonoids (apigenin, luteolin, and 7-O-methylwogonin)	It suppresses oxidative stress and inflammation responses	(27)

4. Recent research studies on herbal hepatoprotectives

In a recent study, it has been reported that thirteen flavonoids out of investigated ninety-six flavonoids were significantly inhibit organic cation transporter 1, which is related with cationic drug induced liver injury. All thirteen flavonoids exhibit more than fifty percent inhibition of transporter, with α-naphthoflavone, apigenin, 6-hydroxyflavone, luteolin, and isosilybin showing the strongest transportor inhibitory action and highest hepatoprotective action (28). In another study, oxidative stress and apoptosis induced by Aflatoxin B1 (AFB1) is another cause of hepatotoxicity. Radix Bupleuri (RB) and its extracts (RBE) has shown significant hepatoprotective activity in perkin ducks (as experimental model). *In vitro* findings in study shows improved hepatocyte morphology, reduced reactive oxygen species levels. *In vivo* results reveals significant alterations in biochemical parameters (enzymatic levels), protein levels (29). Further, soyasaponin Bb in *Abrus cantoniensis* is known for its anti-fibrotic and hepatoprotective action (30).

5. Conclusion

While phytochemicals from herbs such as *Silybum marianum* and *Phyllanthus niruri* have long been recognized for their hepatoprotective properties owing to their antioxidant, anti-inflammatory, and antiviral properties, there remains a critical need for comprehensive scientific evaluation of their efficacy and safety. The promising contributions of these medicinal plants to human health highlight the importance of continued collaboration among pharmacists, ethnobotanists, and researchers to employ modern research techniques and clinical studies. By doing so, we can unlock the full potential of these natural agents in promoting liver health and develop evidence-based therapeutic strategies.

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Exploring the nexus of tradition and scientific thought: The Convergence of Ayurveda and phytopharmaceuticals

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Abstract

Herbal medicines are widely regarded as a significant alternative to modern allopathic treatments, with a long history of use in addressing diverse healthcare needs. Majority of population in developing nations relies on herbal remedies for treating various ailments. Despite the popularity of India as largest producers of medicinal plants, only a limited number of medicinal herbs have undergone scientific evaluation for their therapeutic potential, highlighting an unmet need for the discovery and development of Phytopharmaceutical drugs. Thus, Phytopharmaceuticals is the Bridge of Ancient wisdom with modern medicine. This modern approach highlights the value of evidence- based medicine and the potential for creating potent medication with precise pharmacological effects.

Keywords: Ayurveda, Phytopharmaceuticals, Case studies

1. Introduction

Ayurveda is an ancient system of medicine rooted in India that seeks to promote balance in body, spirit and mind. Ayurvedic principles include balancing of Body's three doshas i.e Vata, Pitta and Kapha- each of which represents elements and energies within the body. Central to Ayurveda, is the use of Plant- based medicines, which include herbs, minerals and also animal products. These medicinal plants are often referred to as "Phytopharmaceuticals" when used in scientific research and regulatory standards showing potential of isolation of specific bioactive compounds from plants for treatment of diseases.

2. Ayurveda: India's timeless knowledge system

Ayurveda is the science of life that helps in health maintenance from ancient time (1). Remarkably, Ayurveda tends to cure various chronic conditions like allergic reactions, skin diseases, arthritis, cancer, neuromuscular diseases asthma and obesity that are untreatable by other medical systems (2). Originating over 5,000 years ago, Ayurveda combines natural remedies, lifestyle practices, and a deep understanding of human physiology to prevent illness. Ayurveda remains a powerful system that continues to gain renewed global interest that focuses on wellness and preventive care.

3. Phytopharmaceuticals: A modern approach to plant based medicine

Phytopharmaceutical drug is defined as purified and standardized fraction with defined minimum four

bioactive or phytochemical compounds of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include administration by parenteral route (3). Phytopharmaceuticals integrate traditional herbal knowledge with pharmaceutical practices and modern scientific research. It focuses on the identification, isolation and standardization of active moieties obtained from specific plants.

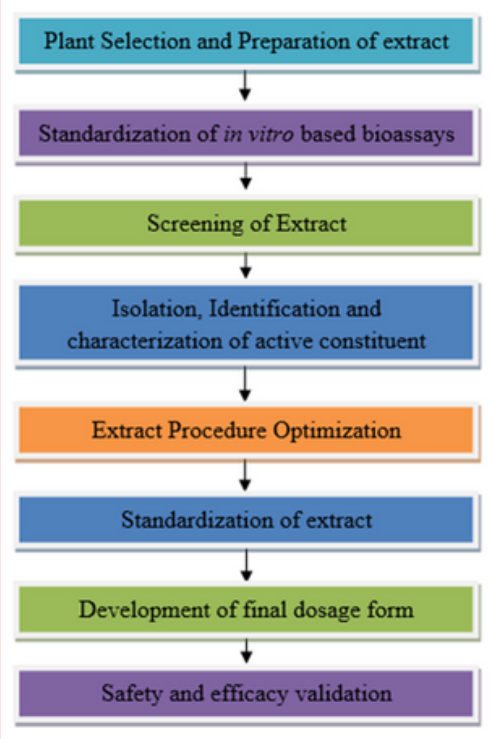

Figure 1. Phytopharmaceutical development process

4. Commutuality: Ayurvedic principles and phytopharmaceutical research

A traditional medicine serves to be a wealth of knowledge and ancient wisdom. Traditional medicinal system integrated with modern healthcare needs a strong scientific validation to ensure safety and efficacy of herbal drugs (4).

5. Scientific validation of herbal remedies: The role of phytopharmaceuticals

World Health Organization (WHO) has developed Good Manufacturing Practices (GMP) guidelines series for traditional medicines that aim to produce basic criteria for evaluating the quality, efficacy and safety of herbal remedies that aid to the national regulatory authorities, scientific departments and manufacturers of product development. The guidelines established by the U.S, FDA, the European Medicines Agency and Indian regulatory authorities are fundamentally aligned, as they are all shaped by principles set forth in the WHO guidelines (5). The use of ASU (Ayurveda, Siddha and Unani) drugs was approved by the Department of AYUSH and other regulatory authorities as per the requirements in India. And the Phytopharmaceuticals are under the purview of the Central Drugs Standard control Organization (CDSCO), Ministry of Health and Family Welfare, Govt. of India, 2015 marked as per Phytopharma guidelines. This gazette notification states that for Phytopharmaceuticals there is scientific research data submission requirement that describes the safety, quality and efficacy of an herbal preparation for evaluation.

6.Case studies: Ayurvedic remedies transformed into phytopharmaceuticals

Phytopharmaceuticals are refined plant- based products, which are standardized to get active components, ensuring their consistent therapeutic effects. Ayurvedic remedies have undergone significant transformation through scientific research, resulting in Phytopharmaceuticals. Some important phytopharmaceuticals and their therapeutic uses are listed in Table 1.

Table 1. List of some important phytopharmaceuticals

S.No.	List of Phytopharmaceuticals	Common name/ Biological name	Therapeutic Uses	Ref
1.	Curcumin	Turmeric/ *Curcuma longa*	Anti-inflammatory and antioxidant properties	(6)
2.	Withanolides	Ashwagandha/ *Withania somnifera*	Managing stress, anxiety and cognitive impairment	(7)
3.	Monoterpenes, Diterpenes, triterpenic acids	Boswellia/ *Boswellia serrata*	Anti inflammatory and analgesic properties	(8)
4.	Guggulipid	Guggul/ *Commiphora mukul*	Lipid lowering agent	(9)
5.	Artemisinin	*Artemisia annua*	Antimalarial	(10)
6.	Ginsenosides	Korean ginseng/ *Panax ginseng*	Anti-inflammatory,antioxidant and immunomodulator	(11)
7.	Digoxin	Woolly foxglove/ *Digitalis lanata*	Cardiotonic	(12)
8.	Morphine	Opium/ *Papaver somniferum*	Analgesic	(13)
9.	Quinine	Loxa bark/*Cinchona ledgeriana*	Antimalarial	(14)
10.	Reserpine & Serpentine	Indian snake root/ *Rauwolfia serpentine*	Antihypertensive and antipsychotic	(15)
11.	Azadirachtin	Neem/ *Azadirachta indica*	Anti-inflammatory, antimicrobial, insecticidal	(16)

These case studies illustrates how plant based medicines have been validated through scientific research, leads to development of safe and effective phytopharmaceuticals.

7. Challenges in convergence: Bridging knowledge system

Integrating Ayurveda with modern Phytopharmaceutical research presents several challenges. The scientific and methodological divergence creates obstacles in bridging the gap between traditional Ayurvedic system and modern phytopharmaceuticals. Ayurveda follows holistic principles while modern processing involves

extraction and purification to yield consistent active compound level by targeting specific biochemical pathways. Secondly, differences in Standardization and validation as Phytopharmaceuticals often comprises the identification and isolation of specific bioactive compounds from plants by ensuring standardized dosing and formulation while Ayurvedic remedies often utilizes whole plant matrices and enfolds a range of plant components causing synergistic interactions. Safety Assessment also creates obstacles. Rigorous pre clinical and clinical trials, detection of potential adverse effects and drug interactions are included in modern scientific research while Ayurvedic medicines might not always perform the same safety testing procedure. Some of the factors like plant sourcing, seasons also lead to variations in active compounds concentrations. A Regulatory and Intellectual Property right further obstructs the convergence. Majority of Ayurvedic medicines are based on traditional knowledge and ancient texts, posing challenges for patenting and IPR's while Phytopharmaceuticals meet the safety and efficacy standards by undergoing extensive clinical testing (17-18). Hence, efforts are required for creating effective Phytopharmaceuticals that are scientifically validated and based on Ayurvedic principles.

8. Regulatory framework: Navigating traditional and modern medicine

Taking an idea of global trends and opportunities in plant based medicines, Government of India has amended the Drugs and Cosmetics Act, 1940 and Rules 1945 to add newer category of Phytopharmaceutical drugs. This gazette notification outlines the regulatory framework for phytopharmaceuticals. It specifies the requirements for submitting scientific data to serve the quality, safety and efficacy of herbal drugs or similar chemical compounds, supporting their evaluation and approval for marketing. These regulations allow the development of new drugs using advanced techniques of solvent extraction, fractionation and modern methods of formulations. The regulatory standards for these drugs categories are aligned with those of China, USA and other such countries regulations involved in scientific evaluation (17).

In India, Healthcare policy decisions are primarily driven by opinions and often overlook regional variations in socioeconomic conditions, culture, literacy levels, population characteristics and other such relevant factors.

9. Future prospects: Unlocking the potential of Ayurvedic phytopharmaceuticals

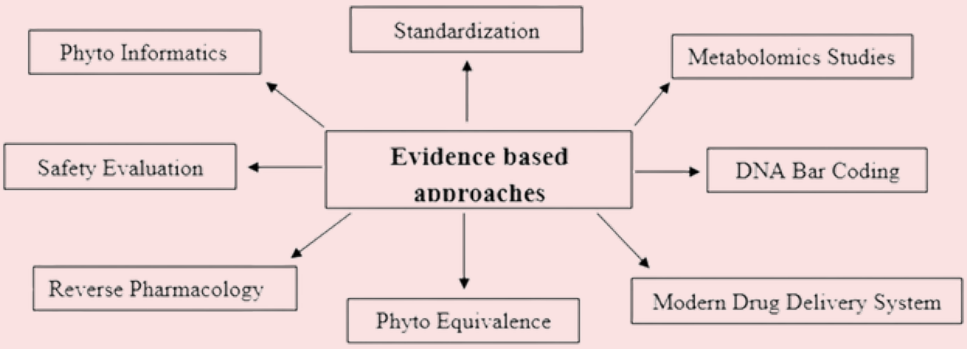

Figure 2. Techniques inspired by Traditional medicinal knowledge

The future of Ayurveda and Phytopharmaceuticals holds vast potential within the contemporary healthcare as modern science continues to explore and validate traditional remedies. By integrating Ayurvedic knowledge with rigorous clinical research, there is great promise for novel therapies that offer natural, holistic solutions to health challenges, contributing to both preventive and therapeutic care on global scale (19).

10. Conclusion: Towards a harmonious integration of tradition and science

Traditional medicines encompass the collective Ethnomedicinal knowledge, indigenous practices and skills of various cultures. So, an urgent requirement has arisen to secure the quality, safety and efficacy effectiveness of traditional medicines to phytopharmaceuticals or products obtained by drug development research. In today's world, most of the countries complementarily use modern as well as traditional system of medicine. Efforts have been undertaken to streamline the evaluation

and quality control processes for botanical preparations in drug discovery. To achieve precise identification and authentication of herbs, it is essential to prevent any admixtures or adulteration in the botanical preparations. For quality assurance, proper identification of plant is crucial for verification, which ultimately guarantees both safety and effectiveness. In summary, by further exploring the synergy between tradition and science, we open up a wider range of healing possibilities that benefit individuals and societies globally.

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Phytopharmaceuticals: India's path to global leadership

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Abstract

Phytopharmaceuticals, derived from plant sources, are gaining global popularity as consumers shift toward natural remedies. India, with its rich biodiversity and traditions in Ayurveda, Unani, and Siddha, plays a key role in this market, which was valued at USD 83 billion in 2019 and growing at 6.5% CAGR. Government initiatives like the Ministry of AYUSH and Phytopharmaceutical Drug Guidelines (2015) promote quality and standardization. Despite challenges in regulation and competition with synthetic drugs, India's strong research potential and public-private collaborations position it well for growth in the global phytopharmaceutical industry.

Keywords: Phytopharmaceuticals, Ayurveda, Natural remedies, Standardization, Biodiversity

1. Introduction

Phytopharmaceuticals, derived from botanical sources, represent a vital component of the modern healthcare system, particularly in the context of rising consumer preference for natural, plant-based medicines. With a growing awareness of the adverse effects of synthetic drugs, patients are increasingly turning towards herbal remedies that offer both efficacy and safety. Globally, the phytopharmaceutical industry is witnessing rapid growth, fueled by the increasing demand for holistic and natural health solutions. In this context, India stands out as a key player due to its rich biodiversity and the age-old tradition of herbal medicine deeply rooted in Ayurveda, Unani, and Siddha systems. This review explores the immense potential of India's phytopharmaceutical sector, focusing on its strengths, current trends, challenges, and opportunities for future growth (1).

2. Global trends in phytopharmaceuticals

The global phytopharmaceutical market is poised for exponential growth, driven by consumers' growing inclination toward natural products. Studies suggest that the global market size for herbal medicine was valued at approximately USD 83 billion in 2019 and is expected to grow at a compound annual growth rate (CAGR) of over 6.5% through 2027. As consumers become more health-conscious and wary of the side effects of synthetic drugs, the demand for natural remedies, dietary supplements, and functional foods is increasing (2).

Regions such as North America and Europe have seen a notable rise in the demand for phytopharmaceuticals, spurred by government policies that promote the use of complementary and alternative medicine. In the United States, for instance, the Dietary Supplement Health and Education Act (DSHEA) regulates herbal supplements, contributing to the rapid growth of the industry. Similarly, the European Medicines Agency (EMA) has established specific guidelines for the approval of traditional herbal medicinal products (3).

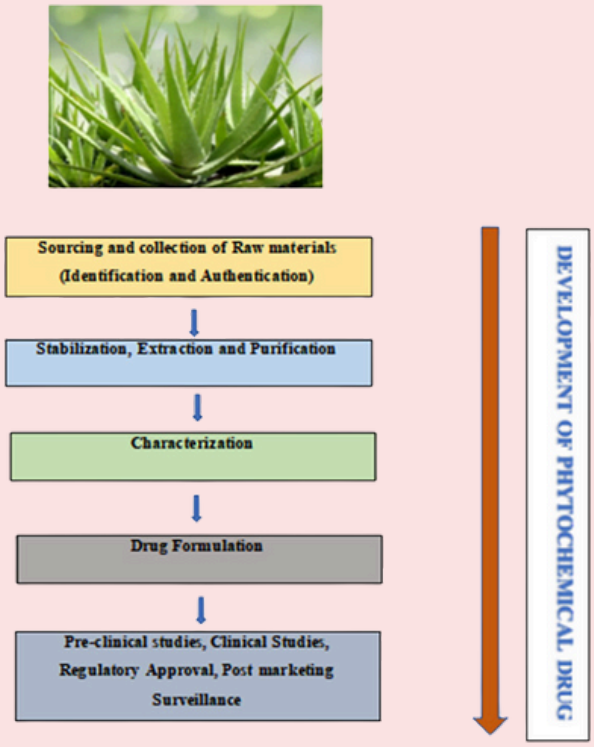

Figure 1. Development of Phytochemical drug

3. Indian government initiatives

Recognizing the potential of phytopharmaceuticals, the Indian government has initiated several measures to promote the sector. The Ministry of AYUSH (Ayurveda, Yoga, Naturopathy, Unani, Siddha, and Homoeopathy) plays a pivotal role in advancing the research, education, and regulation of traditional medicine systems.

The government's focus on promoting phytopharmaceuticals is reflected in the recent Phytopharmaceuticals Drug Guidelines, which facilitate the clinical development of phytopharmaceutical drugs by addressing aspects such as safety, efficacy, and manufacturing standards. However, challenges remain in terms of regulatory clarity, standardization, and the development of clinical data that is on par with synthetic pharmaceuticals (3).

3.1. Ministry of AYUSH

The Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy), established in 2014, is a pivotal government body tasked with promoting and regulating traditional systems of medicine in India, including phytopharmaceuticals. This ministry plays a central role in:

- **Policy development:** The Ministry formulates policies aimed at enhancing the use of phytopharmaceuticals within India's healthcare system. It seeks to integrate these traditional systems with modern healthcare and ensure that phytopharmaceuticals meet global safety, efficacy, and quality standards.
- **Research support:** Through various research councils like the Central Council for Research in Ayurvedic Sciences (CCRAS) and the Central Council for Research in Unani Medicine (CCRUM), the ministry supports research into medicinal plants and traditional formulations, laying the groundwork for phytopharmaceutical development.
- **Pharmacopoeia development:** The Ministry of AYUSH has published the Ayurvedic Pharmacopoeia of India, which serves as a guide for the quality control and standardization of Ayurvedic drugs and herbal products. This is crucial for the phytopharmaceutical sector, as it provides a foundation for developing plant-based drugs with consistent efficacy and safety (4).

3.2. National AYUSH mission (NAM)

The National AYUSH Mission (NAM) was launched in 2014 to promote traditional medicine systems

across India, with a special focus on infrastructure development, capacity building, and integration of AYUSH with mainstream healthcare systems. NAM plays a crucial role in the phytopharmaceutical sector by:

- **Infrastructure development:** NAM supports the establishment and upgrading of AYUSH institutions, ensuring that they are equipped to conduct research, development, and education in traditional medicine and phytopharmaceuticals.
- **Medicinal plant cultivation:** NAM encourages the cultivation of medicinal plants through subsidies and support to farmers. It aims to ensure a steady supply of raw materials necessary for producing phytopharmaceuticals, which is critical for both domestic use and export.
- **Public health integration**: NAM promotes the integration of AYUSH systems into the public healthcare framework. This not only increases the accessibility of traditional medicine and phytopharmaceuticals but also boosts their credibility and acceptance (5).

3.3. Phytopharmaceuticals drug guidelines (2015)

One of the landmark initiatives by the Indian government to support the growth of phytopharmaceuticals was the introduction of the Phytopharmaceuticals Drug Guidelines in 2015 under the Drugs and Cosmetics Act.

- **Standardization and quality control:** These guidelines outline the regulatory framework for plant-based medicines, ensuring that phytopharmaceuticals are standardized in terms of quality, safety, and efficacy. This includes the development of well-characterized extracts and formulations.
- **Safety and efficacy testing:** The guidelines ensure that phytopharmaceuticals undergo rigorous preclinical and clinical testing, similar to synthetic drugs. This enhances the credibility of these products and aligns them with international standards.
- **Manufacturing standards:** The guidelines emphasize good manufacturing practices (GMP) for phytopharmaceuticals, ensuring that they are produced in controlled environments that maintain product safety and quality (6).

3.4. National medicinal plants board (NMPB)

The National Medicinal Plants Board (NMPB) was established in 2000 under the Ministry of AYUSH to promote the conservation, cultivation, and sustainable utilization of medicinal plants, which are essential for the development of phytopharmaceuticals. The NMPB focuses on:

- **Conservation efforts:** NMPB promotes the sustainable harvesting and conservation of medicinal plants, ensuring that rare and endangered species are preserved while also supporting the demands of the growing phytopharmaceutical industry.
- **Support for cultivation**: The board provides financial support to farmers and other stakeholders involved in the cultivation of medicinal plants. This initiative helps ensure a steady supply of high-quality raw materials for the production of phytopharmaceuticals.
- **Market development:** NMPB actively works on developing domestic and international markets for Indian medicinal plants and products derived from them. This helps boost the export potential of Indian phytopharmaceuticals, contributing to the overall growth of the sector (7).

3.5. Scheme for development of botanical drugs

The Indian government, through the Ministry of AYUSH and other associated bodies, has introduced schemes specifically aimed at fostering the development of botanical drugs and phytopharmaceuticals. These schemes focus on:

- **Research and development (R&D):** Funding is provided to research institutions, universities, and industries involved in the R&D of botanical drugs. The goal is to encourage the identification and development of new phytopharmaceuticals from India's rich biodiversity of medicinal plants.
- **Clinical trials support:** The government is increasingly focusing on supporting clinical trials for phytopharmaceutical products, helping these products to meet international safety and efficacy standards. Clinical trials are crucial for validating the therapeutic claims of these products and improving their marketability. (8)

3.6. Atmanirbhar Bharat (Self-Reliant India) initiatives

As part of the broader Atmanirbhar Bharat initiative to boost India's self-reliance in key sectors, the government has also encouraged the domestic production and global promotion of Indian herbal medicines and phytopharmaceuticals.

3.7. Biotechnology initiatives in phytopharmaceuticals

The Department of Biotechnology (DBT) under the Ministry of Science and Technology has also played a role in the phytopharmaceutical industry by supporting research in plant biotechnology.

- **Bioprospecting programs:** DBT has launched several bioprospecting programs aimed at discovering new medicinal plants and compounds that can be developed into phytopharmaceuticals. These programs focus on exploring India’s biodiversity and using advanced scientific methods to validate traditional knowledge.
- **Collaborations with pharma:** DBT is fostering collaborations between biotechnology firms and pharmaceutical companies to support the commercialization of phytopharmaceuticals (9).

4.Current status of the phytopharmaceutical industry in India

India's phytopharmaceutical industry has grown steadily over the past decade, with several companies producing plant-based medicines and herbal supplements. Leading companies like Dabur, Himalaya, and Patanjali have established a strong presence both domestically and internationally.

The export potential of India's phytopharmaceutical sector is enormous. The country is a major exporter of herbal raw materials, medicinal plants, and finished herbal products to markets like the United States, Germany, and Japan. However, the industry must overcome certain barriers, such as competition from synthetic drugs and the need for standardization to ensure the consistency and quality of products (10).

5.Challenges in the Indian phytopharmaceutical industry

Despite its potential, the Indian phytopharmaceutical industry faces several challenges. One of the primary issues is the lack of standardization and quality control. Unlike synthetic drugs, which undergo stringent testing and regulatory approval, many herbal products lack standardized formulations and consistent efficacy.

Moreover, intellectual property issues pose another challenge. Many of India's traditional herbal formulations are part of the public domain, making it difficult to patent or protect these products internationally. Competing with synthetic pharmaceuticals, which are often more standardized and faster-acting, also presents a hurdle for the widespread adoption of phytopharmaceuticals (11).

6. Opportunities for growth

The future of India's phytopharmaceutical industry lies in research and development (R&D) and the integration of modern scientific techniques with traditional knowledge. Biotechnology plays a crucial role in improving the extraction, standardization, and delivery mechanisms of plant-based drugs. Clinical research and trials are essential to validate the therapeutic claims of phytopharmaceuticals, and India must invest in this area to gain global recognition (12).

7. India's journey to global leadership in phytopharmaceuticals

India has significant potential to lead in the field of phytopharmaceuticals, with its rich plant biodiversity and deep-rooted tradition in herbal medicine. To harness this advantage fully and position itself as a global leader, India could focus on several strategic areas that emphasize sustainable practices, scientific validation, and regulatory excellence (13-16).

Table 1. In-depth of critical steps in India's journey in phytopharmaceuticals (13-16)

Strategy	Key Points
1. Utilizing Rich Biodiversity	Involve local communities and collaborate with organizations like the NMPB for sustainable harvesting.
2. Merging Traditional Knowledge with Scientific Research	Integrate Ayurveda and Siddha knowledge with scientific validation. Agencies like CSIR and Ministry of AYUSH are working on research for plant-based treatments.
3. Increasing Research and Development Investments	Boost R&D funding through government support (e.g., AYUSH Ministry, CSIR's Phytopharmaceutical Mission).
4. Strengthening Regulatory Standards	Align with international standards (e.g., FDA, EMA), ensure clinical testing and quality control, and achieve certifications (e.g., GMP, GAP) to ensure safety and quality.
5. Scaling Production and Focusing on Quality Control	Develop labs to standardize potency and purity, ensuring products meet international quality standards.
6. Expanding into International Markets	Leverage growing global demand for natural health products in markets like the U.S., Europe, and Japan
7. Fostering Innovation and Protecting Intellectual Property	Protect IPR by creating a patent framework for unique formulations and methods, preventing unauthorized use.
8. Building a Skilled Workforce	Collaborate with educational institutions to offer specialized programs, ensuring industry demand for trained professionals.

8. Conclusion

India's journey toward becoming a global leader in phytopharmaceuticals is well within reach. By leveraging its rich natural resources, enhancing research capabilities, ensuring regulatory excellence, and expanding international outreach, India can position itself as a trusted provider of effective, high-quality phytopharmaceuticals. With a comprehensive strategy that balances innovation, tradition, and quality, India stands poised to make a significant impact in the global natural health industry.Phytopharmaceuticals offer immense potential for India, not only as a means of preserving its traditional medicinal heritage but also as a driver of economic growth and global leadership in the natural healthcare sector. By focusing on quality control, regulatory clarity, and R&D, India can overcome existing challenges and capitalize on the growing global demand for herbal medicines. With the right strategies in place, India can establish itself as a leader in the global phytopharmaceutical market.

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Phytopharmaceuticals in India: A Comprehensive SWOT Analysis and Market Overview

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Abstract

India, with its rich heritage of traditional medicine, particularly ayurveda, siddha, and unani systems, has emerged as a global leader in the phytopharmaceutical sector. This article presents a comprehensive SWOT analysis of the phytopharmaceutical market in India, highlighting its strengths, weaknesses, opportunities, and threats. Additionally, it provides a market analysis that underscores the potential for growth and expansion in both domestic and international markets. The findings suggest that while the phytopharmaceutical industry in India is poised for significant growth, strategic investments in research, quality control, and regulatory compliance are essential for sustainable development.

Keywords: Phytopharmaceuticals, India, Industry, SWOT analysis.

1. Introduction

The therapeutic potential and low side effects of phytopharmaceuticals purified and standardised extracts from medicinal plants have drawn a lot of attention in comparison to synthetic medications. Under the 1940 Drugs and Cosmetics Act, the Indian government set laws for phytopharmaceuticals, opening the door for their development and commercialisation. In order to give the reader a deeper understanding of the drug industry, this article will analyse the historical background of phytopharmaceuticals in India, the current state of the Indian phytopharmaceutical market using a thorough SWOT analysis, as shown in figure 1, and a market assessment (1,2).

2. Historical background of phytopharmaceuticals in India

India is deeply rooted in the country's rich tradition of herbal medicine, which dates back thousands of years. Ancient texts such as the vedas, particularly the atharva veda, contain references to various 1medicinal plants and their therapeutic uses. The knowledge and use of herbal therapies have been significantly influenced by ancient medical systems like as Ayurveda, Siddha, and Unani.

One of the world's oldest medical systems, Ayurveda, places a strong emphasis on using plant-based medicines to promote health and healing. It categorizes herbs based on their properties and effects on the body, promoting a holistic approach to health. Siddha medicine, primarily practiced in south india, also utilizes a variety of herbs and minerals, focusing on the balance of bodily humors.

The Unani system, influenced by Greek and Arab medicine, incorporates herbal treatments alongside dietary and lifestyle recommendations. These traditional practices have been passed down through generations, with practitioners relying on empirical knowledge and ancient texts.

As interest in the scientific study of medicinal plants grew throughout the British colonial era in the 19th and 20th centuries, botanical gardens and research institutes were established. This period marked the beginning of formal documentation and classification of Indian medicinal plants. Post-independence, the Indian government recognized the importance of traditional medicine and initiated efforts to integrate it with modern healthcare. The establishment of the ministry of AYUSH in 2014 further solidified the role of traditional systems in the national health policy.

A worldwide movement towards natural and holistic health solutions has sparked a renewed interest in phytopharmaceuticals in recent years. The regulatory framework for phytopharmaceuticals has evolved, with the introduction of guidelines to ensure quality, safety, and efficacy, aligning traditional knowledge with modern scientific standards. Today, India stands as a leader in the global phytopharmaceutical market, leveraging its biodiversity and traditional knowledge to develop innovative herbal products. The integration of modern research methodologies with ancient practices continues to enhance the credibility and acceptance of phytopharmaceuticals both domestically and internationally (3, 4).

Figure 1. SWOT analysis of phytopharmaceuticals in India

3. Strength

3.1. Rich biodiversity

India boasts one of the richest biodiversity hotspots in the world, with over 8,000 documented medicinal plants. This vast array of flora provides a solid foundation for the development of phytopharmaceuticals. Traditional texts like the Vedas and Charaka Samhita not only document these plants but also their therapeutic uses, creating a wealth of knowledge that can be harnessed for modern applications. The diversity of species allows for the exploration of various phytochemicals, which can lead to the discovery of new drugs and treatments (5,6).

3.2. Established traditional systems

The long-standing practices of ayurveda, siddha, and unani medicine offer a robust framework for phytopharmaceutical development.These systems, which emphasise a holistic approach to health that takes into account one's physical, mental, and spiritual well-being, have been in use for millennia. The established methodologies and therapeutic principles provide a credible basis for developing new phytopharmaceuticals, as they are backed by historical usage and cultural acceptance (7).

3.3. Regulatory framework

The legitimacy and safety of these products are increased by the implementation of certain regulations for phytopharmaceuticals, such as the changes to the laws governing medications and cosmetics. This regulatory framework ensures that phytopharmaceuticals meet stringent quality standards, which is crucial for building consumer trust. By aligning with international standards, Indian phytopharmaceuticals can gain a competitive edge in the global market (8).In India, CDSCO is the main regulatory agency in charge of phytopharmaceuticals. The regulatory procedure for phytopharmaceuticals in India is depicted

in Figure 2. The application (form 44), which contains comprehensive details on the product's formulation, manufacturing procedures, and quality control measures, is submitted to CDSCO to start the regulatory process. If deemed necessary, clinical trials must be conducted to gather data on safety and efficacy. Following a thorough review of the submitted data, CDSCO will either approve or reject the application based on compliance with established standards. Once approved, the product receives market authorization, allowing it to be sold commercially. Post-marketing surveillance is mandatory to monitor any adverse effects reported by consumers, ensuring ongoing compliance with safety standards. By adhering to these stringent regulatory requirements, Indian phytopharmaceuticals can not only enhance their credibility but also foster greater consumer confidence in herbal products as viable alternatives to synthetic medications (13).

3.4. Growing global demand

The usage of herbal remedies has grown in popularity in recent years due to the ineffectiveness of contemporary treatments for chronic illnesses and their unintended, serious side effects. Prototype chemicals extracted and found in plants have been used to create a variety of contemporary medications and their synthetic counterparts. Due to consumer knowledge of health and wellbeing, there is a growing global trend towards natural medicines. Table 1 lists a few phytopharmaceuticals and their therapeutic advantages. It is anticipated that the worldwide market for phytopharmaceuticals would expand dramatically as people look for synthetic medicine substitutes. For Indian producers, this rising demand offers a profitable chance to broaden their customer base and serve global markets, especially in areas where herbal therapy is becoming more popular (6).

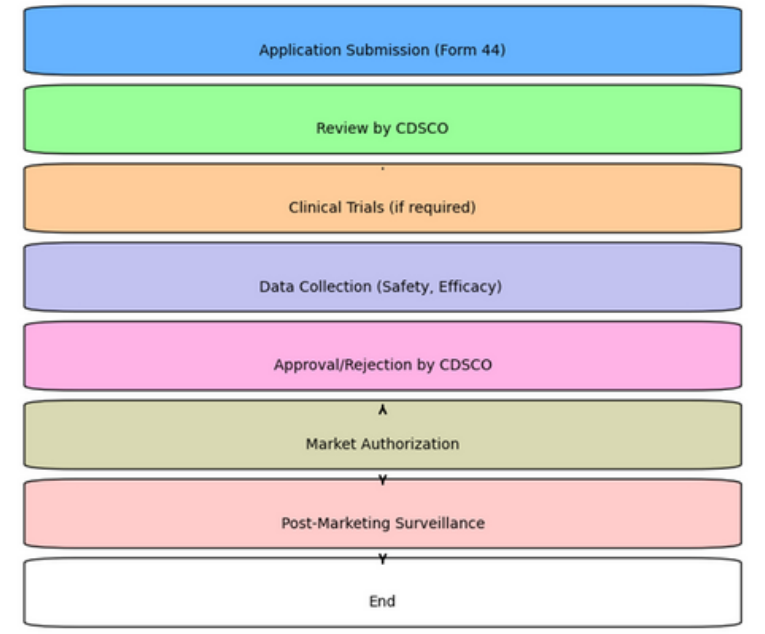

Figure 2. Regulatory process for phytopharmaceuticals in India

Table 1. The list of few pharmaceuticals and their therapeutic benefits.

Phytochemical	Botanical name	Therapeutic benefits
Curcumin	*Curcuma longa*	Anti-inflammatory, antioxidant
Resveratrol	*Vitis vinifera*	Cardiovascular health, anti-aging
Quercetin	*Allium cepa*	Antioxidant, anti-inflammatory

Flavonoids	Various	Heart health, anti-cancer
Lycopene	*Solanum lycopersicum*	Prostate health, antioxidant
Catechins	*Camellia sinensis*	Weight loss, heart health
Silymarin	*Silybum marianum*	Liver protection, antioxidant
Gingerol	*Zingiber officinale*	Anti-nausea, anti-inflammatory
Allicin	*Allium sativum*	Antimicrobial, heart health
Berberine	*Berberis vulgaris*	Blood sugar regulation, antimicrobial
Thymoquinone	*Nigella sativa*	Anti-inflammatory, antioxidant
Chlorophyll	Various	Detoxification, wound healing
Beta-carotene	*Daucus carota*	Vision health, antioxidant
Omega-3 fatty acids	Various	Heart health, anti-inflammatory
Tannins	Various	Antioxidant, antimicrobial
Lutein	*Spinacia oleracea*	Eye health, antioxidant
Apigenin	*Matricaria chamomilla*	Anxiety reduction, anti-inflammatory
Eugenol	*Syzygium aromaticum*	Pain relief, antimicrobial
Rosmarinic acid	*Rosmarinus officinalis*	Anti-inflammatory, antioxidant
Curcumin glucuronide	*Curcuma longa*	Enhanced bioavailability of curcumin

4. Weakness

4.1. Lack of standardization

The variation in the effectiveness and quality of herbal medicines is one of the major issues facing the phytopharmaceutical sector. The absence of standardized manufacturing processes can lead to inconsistencies in product quality, which undermines consumer trust. Without established protocols for cultivation, harvesting, and processing, the reliability of herbal products can be compromised, affecting their therapeutic outcomes (2,9).

4.2. Limited research and development

Despite the potential of phytopharmaceuticals, there is a notable lack of investment in research and development. Many herbal products lack robust clinical data to support their efficacy and safety, which can hinder market acceptance. The need for more scientific studies and clinical trials is critical to validate the claims made by manufacturers and to enhance the credibility of phytopharmaceuticals in the eyes of healthcare professionals and consumers (4,10).

4.3. Market fragmentation

The presence of numerous small players in the phytopharmaceutical market can lead to inconsistent quality and branding challenges. This fragmentation makes it difficult for consumers to identify reliable products, as there is often a lack of clear differentiation between brands. Additionally, small manufacturers may struggle to compete with larger companies that have more resources for marketing and quality assurance (11).

4.4. Adulteration and misidentification

The risk of adulteration and misidentification of raw materials poses a significant challenge to the industry. This issue can arise from confusion over vernacular names and inter-species variation in different geographical regions. Such practices not only compromise product quality but also pose health risks to consumers, leading to potential legal and reputational repercussions for manufacturers (12).

5. Opportunities

5.1. Expanding international markets

The growing acceptance of herbal medicines in developed countries presents significant opportunities for export. Indian phytopharmaceuticals can tap into these markets by emphasizing quality, efficacy, and the rich heritage of traditional medicine. By establishing partnerships with international distributors and participating in global trade fairs, Indian companies can enhance their visibility and market presence (4).

5.2. Integration with modern medicine

Collaborations between traditional and modern medical systems can enhance the credibility and acceptance of phytopharmaceuticals. By integrating phytopharmaceuticals into conventional healthcare practices, healthcare providers can offer holistic treatment options that combine the best of both worlds. This integration can also lead to increased research funding and support from the medical community (10).

5.3. Government initiatives

The Indian government has been actively promoting the use of traditional medicine through various initiatives, including funding for research and development. The guidelines for conducting clinical trials or importing or manufacturing phytopharmaceutical drugs in the nation are outlined in Appendix 1b of the Drugs and Cosmetics Act 1940 and Rules 1945. These guidelines cover basic information, pharmacognostic data, formulation, stability, safety, toxicity data, and human or clinical pharmacology data. Since there is no separate regulation for phytopharmaceutical drugs in other countries, India, which is well-known for its abundance of herbal medicine, led the global regulatory system by regulating these drugs. Table 2 compares the regulations of India's phytopharmaceutical drugs with those of developed and developing nations. Supportive regulations targeted at boosting the phytopharmaceutical sector might result in more investment and growth as the market demand for Indian goods and phytopharmaceuticals in India grows daily. Government-backed programs can also facilitate training and education for practitioners, ensuring a skilled workforce to support the industry (2).

5.4. Rising health consciousness

The demand for natural and organic products is being driven by customers' growing knowledge of health and wellness. This trend presents a significant opportunity for the phytopharmaceutical market to expand its consumer base. By aligning product offerings with consumer preferences for sustainability and natural ingredients, companies can attract a broader audience and enhance brand loyalty (10).

Table 2. Comparison of the regulatory processes for phytopharmaceuticals across different countries.

Aspect	India	United states	Europe
Regulatory body	Central drugs standard control organization (CDSCO)	Food and drug administration (FDA)	European medicines agency (EMA)
Regulation framework	Schedule Y,appendix IB of drugs and cosmetics act	Botanica drug development guidance	Directive 2004/24/EC and directive 2001/83/EC
Application process	Submission of form 44, including safety and efficacy data	New drug application (NDA) and investigational new drug (IND) applications	Traditional use registration, well-established use marketing authorization
Clinical trials	Required if safety and efficacy data are insufficient	Required for NDA approval	Required unless sufficient traditional use evidence exists
Quality control	Standardization and quality control as per GMP guidelines	Detailed botanical raw materials and product specifications	Compliance with pharmacopoeial standards
Approval time	Varies based on data sufficiency and compliance	Typically longer due to comprehensive clinical trial requirements	Can be expedited if traditional use is established
Post-marketing surveillance	Mandatory to monitor adverse effects	Mandatory as part of FDA regulations	Mandatory under EU pharmacovigilance regulations

6. Threats

6.1. Regulatory challenges

Navigating the complex regulatory landscape can be daunting for new entrants in the phytopharmaceutical market. Compliance with stringent regulations can be resource-intensive, potentially deterring small businesses from entering the market. Additionally, frequent changes in regulations can create uncertainty, making it challenging for companies to plan and invest in long-term strategies (1,12).

6.2. Competition from synthetic drugs

The dominance of synthetic pharmaceuticals poses a significant challenge to the growth of phytopharmaceuticals. Many consumers still prefer conventional medications due to their established efficacy and safety profiles. Overcoming this preference requires robust marketing strategies and education efforts to highlight the benefits of phytopharmaceuticals (4,10).

6.3. Market saturation

As more players enter the phytopharmaceutical market, competition may lead to price wars and reduced profit margins. This saturation can make it difficult for companies to differentiate their products and maintain profitability. To survive in a crowded market, companies must innovate and find unique selling propositions that resonate with consumers.

6.4.Consumer scepticism

Despite the growing interest in herbal products, some consumers remain skeptical about their efficacy compared to conventional medicines. Overcoming this skepticism will require robust marketing and education efforts, including transparent communication about the benefits and scientific backing of phytopharmaceuticals. Building trust through testimonials, clinical evidence, and endorsements from healthcare professionals can help mitigate this challenge (2).

7. Market analysis of phytopharmaceuticals in India

India's phytopharmaceutical industry is expanding significantly, mostly due to rising consumer awareness of wellness and health issues and a noticeable trend towards natural and organic goods. Over the next five years, the market is expected to increase at a compound annual growth rate (cagr) of around 15%. A global market estimate of almost $100 billion in 2011 supports this development trend, and as customers look for alternatives to synthetic drugs more and more, the industry is expected to continue expanding (4,10).

Several companies are at the forefront of the phytopharmaceutical market in India, each contributing to the sector's growth through innovative products and strong market presence:

7.1. Himalaya Drug Company: Renowned for its extensive range of herbal products, himalaya has established a robust presence in both domestic and international markets. The company focuses on quality and efficacy, leveraging traditional knowledge and modern science.

7.2. Dabur India Ltd.: Dabur, a leader in the herbal industry, provides a wide variety of goods, such as ayurvedic medications, personal care products, and health supplements. The company's market position is improved by its well-known brand and robust distribution network.

7.3. Patanjali Ayurved: This rapidly growing company has gained immense popularity for its focus on ayurvedic products, capturing a significant market share. Patanjali's marketing strategies and emphasis on natural ingredients resonate well with health-conscious consumers.

7.4. Zandu Pharmaceutical Works Ltd.: Offering a range of goods, including ayurvedic formulations, Zandu has a long history of using herbal therapy. The business is renowned for its traditional methods and dedication to quality.

8. Market segmentation

The phytopharmaceutical market can be segmented based on product type and application:

8.1. Herbal Product type:

- **Herbal supplements:** 40% market share, with a growth rate of 15%.
- **Herbal medicines**: 35% market share, with a growth rate of 12%.
- **Herbal cosmetics:** 25% market share, with a growth rate of 18%.

8.2. Application:

- **Dietary supplements:** products aimed at enhancing health and wellness.
- **Pharmaceuticals:** herbal formulations used for therapeutic purposes.
- **Personal care products:** herbal cosmetics and skincare items.

One major factor driving the demand for natural and organic products is customers' growing health concern. Customers' purchase habits are changing as a result of their increased knowledge of the advantages of herbal treatments. A large variety of phytopharmaceutical goods are now more easily accessible thanks to the growth of e-commerce platforms, which let customers browse and buy items from the comfort of their homes (10).

9. Challenges in the market

Despite the positive outlook, the phytopharmaceutical market faces several challenges:

9.1. Quality control: Ensuring consistent quality across products is crucial for maintaining consumer trust. Companies must invest in quality control measures to prevent adulteration and ensure product efficacy. This includes rigorous testing and adherence to established standards.

9.2. Regulatory compliance: It can be difficult for small and medium-sized businesses (SMEs) to

comply with the regulations put forth by the government. It takes resources and experience to navigate the complicated regulatory environment.

9.3. **Consumer education:** educating consumers about the benefits and proper usage of phytopharmaceuticals is essential for overcoming skepticism and building trust in these products. Misconceptions about herbal products can hinder market growth.

10. Future outlook

The The increasing global demand for herbal products, coupled with supportive government policies, presents a favorable environment for the expansion of the industry. However, addressing the challenges of quality control, regulatory compliance, and consumer education will be critical for the sustainable development of the sector.

10.1. **Investment in R&D:** Companies should prioritize research and development to explore the full potential of phytopharmaceuticals. This includes conducting clinical trials to establish robust clinical data that supports product claims and efficacy.

10.2. **Quality assurance:** Implementing stringent quality control measures will help ensure product consistency and build consumer trust. This may involve adopting international quality standards and certifications.

10.3. **Consumer education campaigns**: Educating consumers about the benefits and proper usage of phytopharmaceuticals can help overcome skepticism and drive demand. Companies can leverage digital marketing, workshops, and informational content to enhance consumer awareness.

10.4. **Collaboration with research institutions:** Collaborating with academic and research institutions can facilitate innovation and the development of new phytopharmaceutical products. Such partnerships can also enhance credibility and provide access to advanced research facilities.

10.5. **Sustainable sourcing:** Emphasizing sustainable sourcing of raw materials can enhance brand reputation and appeal to environmentally conscious consumers. Companies should consider ethical sourcing practices and support local communities involved in herbal cultivation.

By addressing these recommendations, companies can position themselves effectively in the growing phytopharmaceutical market and contribute to the overall development of the sector in India (10,12).

11. Conclusion

India’s phytopharmaceutical sector appears to have a bright future ahead of it, with plenty of room to expand. Phytopharmaceutical market in India holds immense potential for growth, driven by its rich heritage of traditional medicine and increasing global demand for natural products. However, addressing the challenges of standardization, research, and regulatory compliance will be crucial for the sector's success. With strategic investments and a focus on quality, India can solidify its position as a leader in the global phytopharmaceutical market.

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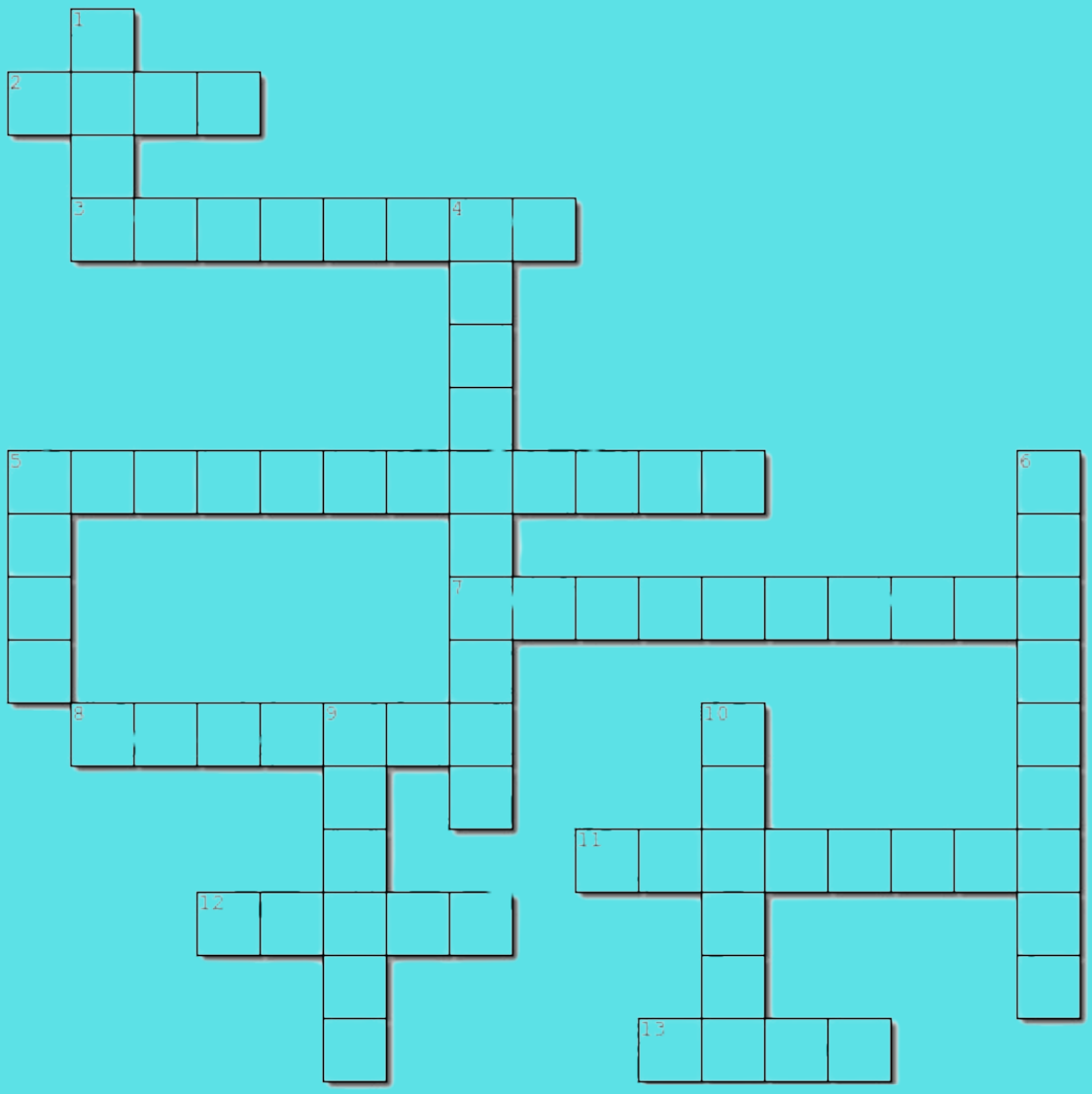
Complete the crossword puzzle below



Across

2. Bioactivity-guided fractionation abbreviated
3. CSIR-CDRI phytopharmaceutical for NAFLD
5. Monograph of Phytopharmaceutical ingredient in IP-2022
7. Multi-enzyme complex used for extraction
8. Commercialized CSIR-CDRI Plant Extract A-4744
11. Patented herbal invention of CSIR-National Botanical Research Institute (NBRI)
12. Indian Medicinal Phytochemical Database Curated for Drug Designing
13. Methodology to assay phytomarkers

Down

1. Enzyme-assisted cold pressing abbreviated
4. Phenolic phytonutrient
5. Technique used for Combinatorial Drug Discovery
6. Commercialized aromatherapy based herbal oil developed by CSIR-CIMAP
9. Manually curated database of Indian Medicinal Plants, Phytochemistry And Therapeutics
10. Xanthophyll with anticancer properties

Answers are on page 226

Phytopharmaceuticals: A sustainable solution for India's healthcare sector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Abstract
Phytopharmaceuticals are scientifically proven herbal medicines that have become important to the Indian Pharmaceutical Industry. India is a leader in this field with its rich biodiversity and traditional medical knowledge. Unlike herbal products, herbal medicines have undergone rigorous standards, clinical trials, and regulatory approvals to ensure their safety and efficacy. The integration of herbal medicine in treatment represents a significant change in safe, effective, and efficient treatment. Known for its rich biodiversity and deep roots in traditional medicines, India is a leader in this field. This review highlights the potential of phytopharmaceuticals in solving health problems and also discusses the advantages over synthetic drugs and suggests the avenues for future development in the Indian health system. (BGR-34, anti-diabetic drug) and Liv.52 (liver health). The appendix demonstrates the potential of the work.

Keywords: Phytopharmaceuticals, Herbal Remedies, Pharmaceutical Industry, Healthcare solutions.

1. Introduction
Phytopharmaceuticals, plant-based derived sources have become one of the most emerging promising frontiers in the pharmaceutical industry in India. These scientifically proven plant based medications comprise both traditional wisdom and contemporary research, utilizing their natural origins to create safer and more comprehensive treatment alternatives. The potential for phytopharmaceuticals is enormous in India, a country with a wide variety of flora and long-standing medical customs. India is uniquely positioned to utilize its natural resources and become a global center for plant-based medicines because of its vast history of using herbal remedies and growing scientific discoveries. Phytopharmaceuticals are poised to play a significant role in fulfilling the growing need for sustainable, natural, and effective healthcare solutions as the globe looks for alternatives to synthetic treatments (1,2).

Figure 1. Types of phytopharmaceuticals

2. What are phytopharmaceuticals?

Phytopharmaceuticals are purely standardized and characterized plant-based active moieties that are used as medicines. Phytopharmaceuticals unlike traditional herbal products, mainly undergo rigorous scientific research, that includes important aspect which are the clinical trials, for validation of their safety and efficacy. These are the new class of drug including with at least four chemical markers and single biomarkers which comes out as an enrich fraction to be used in a drug, not being a part of the Ayurvedic literature. The development of these drugs involves isolating active ingredients from medicinal plants, followed by standardization and testing to meet modern pharmaceutical standards. (3)

Table 1. Key differences between herbal products and phytopharmaceuticals (3)

Parameter	Herbal Products	Phytopharmaceuticals
Standardization	Generally unstandardized	Highly standardized and regulated
Regulatory Approval	Limited regulatory scrutiny	Requires stringent regulatory approval
Clinical Trials	Rarely Conducted	Mandatory for approval
Safety and Efficacy	Based on traditional use	Scientifically validated through clinical trials
Active Ingredients	May contain multiple components	Specific active ingredients isolated and tested
Market Access	Easily accessible in the market	Requires formal registration and approval

3. The growing need for sustainable healthcare solutions

Indian healthcare faces several pressing challenges, including high disease burden, limited access to affordable medicine, and the rise of antimicrobial resistance. Conventional pharmaceutical drugs, while effective, often come with high costs and significant side effects. The sustainability of drug development, in terms of both environmental impact and resource use, is also a growing concern. Phytopharmaceuticals offer a solution that can bridge these gaps through cost efficiency, fewer side effects, and biocompatibility. The use of local plant resources and traditional knowledge reduces production costs. Natural compounds tend to have fewer side effects compared to synthetic drugs. Products of plant origin often show better compatibility with human physiology.

3.1. Sustainable sourcing

Sustainable sourcing is one of the main aspects of phytopharmaceuticals, as it helps to increase environmental stewardship and ensure the long-term viability of plant materials. Many industries in India are currently implementing, or have already implemented, techniques to promote ecological balance, such as selective sustainable harvesting, which allows them to selectively select parts of the plant to be used and leave other plant parts to continue to grow and regenerate. Partnering with indigenous communities and implementing fair trade practices to ensure fair compensation for local harvesters.

3.2. Sustainability aspects of phytopharmaceuticals

3.2.1. Value added product manufacturing from phytopharmaceuticals waste

Waste generation is a part of every other industry whether its chemicals, organic wastes or reusable wastes. Similarly, in the Phytopharmaceutical Industry, the waste generated is in a massive amount due to the usage of various physical and chemical techniques. Out of these phytopharmaceuticals waste produced in tons every year are then categorized as either hazardous or non-hazardous wastes having a potential to be transformed into the value-added product. Examples of such value-added products can be Biofuels, Organic Fertilizers, Animal Feed including poultry and fish feed, Biopolymers, Biomass Production, Nutraceuticals, Bioethanol Production and Essential oils and extracts (7).

3.2.2. Economic impact on sustainability of phytopharmaceuticals

Industries by using such techniques of reformation and reuse of products can result in reduction of operational costs and enhance profitability. Market demand of sustainable products is also increasing day by day inviting environmental conscious customers improving market edge.

Table 2. Key steps in phytopharmaceutical development

Steps	Description
Identification of plant material	Selection of medicinal plants with therapeutic potential
Extraction and isolation	Isolation of active compounds using standardized methods
Characterization of compounds	Chemical and biological characterization of active ingredients
Preclinical studies	Animal testing to evaluate safety and preliminary efficacy
Clinical trials	Human studies to confirm safety, dosage, and therapeutic value

Regulatory submission	Submission of data to regulatory authorities for approval
Manufacturing	Large-scale production under GMP

3.3. India's competitive advantage in phytopharmaceuticals

3.3.1. Rich biodiversity

India is home to approximately 8% of the world's biodiversity, with over 45,000 plant species, many of which have different medicinal properties. This diverse flora provides a distinct benefit for the development of phytopharmaceuticals (8,9).

3.3.2. Traditional knowledge base

The traditional systems of medicine, such as Ayurveda, provide an abundant knowledge reservoir about the therapeutic uses of plants. This indigenous wisdom can guide the selection of plants for developing phytopharmaceuticals (8,9).

3.3.3. Skilled workforce

India has a strong pool of scientists and researchers specializing in pharmacognosy, phytochemistry, and pharmaceutical sciences. This expertise supports the development and validation of plant-based drugs (8,9).

3.3.4. Cost effective production

Lower labour costs and affordable raw materials make India an attractive destination for the large-scale production of phytopharmaceuticals (8,9).

3.4. Challenges faced by the phytopharmaceutical sector

Despite its potential, the development of phytopharmaceuticals in India faces several challenges:

3.4.1. Standardization and quality control

Ensuring the consistent and maintained quality of plant-based raw materials is difficult due to variations in cultivation practices, geographical conditions, and processing methods (10).

3.4.2. Regulatory hurdles

Although a regulatory framework exists, it can be cumbersome, with long approval timelines for new phytopharmaceuticals (10).

3.4.3. Limited research funding

Investment in research and development for phytopharmaceuticals is relatively low, which obstructs the discovery of new drugs and the improvement of existing formulations (10).

3.4.4. Geographical variation in active ingredients

The concentration and composition of various bioactive compounds may differ depending on the soil type, climate and cultivation practices (10).

3.5. Quality, purity and safety of phytopharmaceuticals

The quality, purity and safety of the phytopharmaceuticals are based around and can be studies by assessing certain parameters including:

3.5.1. Type of active constituents

The specific plant or components being used in the preparation of medicines. Phytochemicals can be

made from the whole plant or extracts opted from the same plants. The type of active constituent is crucial because different parts of the plant may contain varying concentrations of active compounds, which can affect the medicine's effectiveness (11).

3.5.2. Number of active constituents

This parameter measures the amount of active chemicals present in the dosage units (e.g., tablets, capsules, liquid preparations). It is important for ensuring that the patient receives the appropriate therapeutic doses in the form of medicines (11).

3.5.3. Drug to extract ratio

It indicates amount of raw material needed to create a specific amount of extracts (11).

3.5.4. Type and concentration of the extraction solvent

The solvent is a type liquid used to extract the active ingredients from the plant material. For example, methanol at 50% concentration is a common solvent used in the extraction process. The choice of solvent and its concentration are critical because they determine which compounds are extracted and in what quantity (11).

4. Successful Indian phytopharmaceuticals: Case studies

4.1. BGR-34: Anti-diabetic drug

BGR-34 is an herbal anti-diabetic medicine developed by the Council of Scientific and Industrial Research (CSIR) and the National Botanical Research Institute (NBRI). It blends extracts from six medicinal plants and has been scientifically validated for its efficacy in managing blood sugar levels (12,13).

4.2. Himalaya's Liv.52: Liver care

Himalaya's Liv.52 is one of the most popular phytopharmaceuticals, known for promoting liver health. It contains extracts from various herbs, such as *Capparis spinosa* and *Cichorium intybus*, which have hepatoprotective properties (12,13).

4.3. Patanjali Ayurved - Divya Swasari Pravahi

Patanjali Ayurved - Divya Swasari Pravahi turned out to be an effective Ayurvedic medicine mainly being used for the treatment of asthma. Consisting of various natural and herbal constituents including Bringharaj (*Eclipta Alba*), Tejpatra *(Cinnamomum Tamala)*, Sonth (*Zingiber Officinale*), Lavang (*Syzgium Aronmaticum*). This medicine is being used for the treatmnts of various other disorders with properties of bronchodilation, antibacterial, anti-inflammatory, mucolytic and antioxidant (12,13).

5. The future of phytopharmaceuticals in India

The future of phytopharmaceuticals in India looks promising, especially with increased global interest in herbal medicines. Several trends are likely to shape the growth of this sector:

5.1. Expansion of the regulatory framework

Improving regulatory workflow and providing incentives for the development of phytopharmaceuticals can boost innovation and market access (14).

5.2. Public awareness and acceptance

Educating healthcare professionals and the public about the benefits and safety of scientifically validated phytopharmaceuticals can increase their acceptance as a mainstream treatment option (14).

5.3.Increased investment in research and development

Greater funding for phytopharmaceutical research will help discover novel drugs and enhance existing formulations. Collaborations between academia, industry, and government bodies will be

crucial in this endeavour. For Example: Most recently, the Department of Pharmaceuticals has also launched a Production Linked Incentive Scheme 2.0, with an expense of Rs 15,000 Crore (~$ 2 Bn), across a huge range of product categories, including phytopharmaceuticals, fostering incentives to be awarded to investors interested in this fast-emerging sector (14).

6. Conclusion

Phytopharmaceuticals represent a unique opportunity for India to leverage its biodiversity and traditional knowledge to develop scientifically validated plant-based medicines. The sector's growth can be accelerated through supportive government policies, increased research investment, and public education. By overcoming challenges such as standardization and regulatory hurdles, India can establish itself as a global leader in the phytopharmaceutical industry, offering natural and effective healthcare solutions to the world.

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The green revolution: Phytopharmaceuticals and India's wellness journey

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Abstract
This essay explores the significant potential of phytopharmaceuticals for India, a country rich in biodiversity and traditional medicinal knowledge. Phytopharmaceuticals, scientifically validated medicinal products derived from plants, represent a promising intersection of traditional wisdom and modern science. The essay discusses India's current regulatory framework, ongoing research efforts, and the substantial market potential in this field. It highlights key opportunities, including leveraging India's vast biodiversity, integrating traditional knowledge with modern scientific methods, and potential economic benefits through job creation and export growth. The essay also addresses challenges such as quality control, clinical trial complexities, intellectual property rights, and environmental concerns. To realize the full potential of phytopharmaceuticals, the paper suggests increased investment in research and development, capacity building, supportive government policies, international collaborations, and the implementation of sustainable practices. By capitalizing on its unique strengths in this sector, India has the opportunity to become a global leader in phytopharmaceuticals, contributing to both national development and global healthcare solutions.

Keywords: Traditional medicinal knowledge, Plant-derived medicines, Regulatory framework, Research efforts, Market potential

1. Introduction

In the realm of modern medicine, there is a growing interest in harnessing the power of nature to address human health concerns. This intersection of traditional knowledge and cutting-edge science has given rise to the field of phytopharmaceuticals. For India, a country with a rich biodiversity and a long history of traditional medicine, phytopharmaceuticals represent not just a promising avenue for healthcare innovation but also a significant economic opportunity. This essay explores the immense potential of phytopharmaceuticals for India, examining the current landscape, opportunities, challenges, and the path forward (1).

2. Understanding phytopharmaceuticals

2.1. Definition and scope

Phytopharmaceuticals, also known as plant-based pharmaceuticals or botanical drugs, are medicinal products derived from plants or plant materials. These products are used for the purpose of curing,

mitigating, treating, or preventing diseases in humans. Unlike traditional herbal remedies, phytopharmaceuticals undergo rigorous scientific testing and are subject to regulatory approval processes similar to conventional pharmaceuticals (2).

2.2. Historical context

The use of plants for medicinal purposes is not new to India. The country's traditional systems of medicine, such as Ayurveda, Siddha, and Unani, have relied on plant-based remedies for thousands of years. This rich heritage of traditional knowledge forms a strong foundation for the development of modern phytopharmaceuticals (3).

Figure 1. Timeline showing the evolution of traditional medicine in India

3. The current landscape of phytopharmaceuticals in India

3.1. Regulatory framework

In recent years, India has taken significant steps to recognize and regulate phytopharmaceuticals. In 2015, the Ministry of Health and Family Welfare introduced a new category of drugs called "phytopharmaceutical drugs" in the Drugs and Cosmetics Rules, 1945. This move provided a clear regulatory pathway for the development and commercialization of plant-based drugs in India (3).

3.2. Research and development

Several Indian research institutions and pharmaceutical companies are actively engaged in phytopharmaceutical research. The Council of Scientific and Industrial Research (CSIR), Indian Council of Medical Research (ICMR), and various universities are at the forefront of this research. Notable successes include the development of anti-diabetic drugs from plants like *Pterocarpus marsupium* and anti-malarial compounds from *Artemisia annua* (3).

Table 1. Major Indian institutions involved in Phytopharmaceutical Research

Institution	Focus Area	Notable Achievements
CSIR	Drug discovery from plants	Anti-diabetic drug from *Pterocarpus marsupium*
ICMR	Clinical trials of herbal formulations	Standardization of Ayurvedic formulations
IIT Bombay	Phytochemical analysis	Novel extraction techniques for bioactive compounds
AIIMS	Clinical studies on herbal drugs	Efficacy studies on traditional remedies

3.3. Market potential

The global market for phytopharmaceuticals is growing rapidly, with projections suggesting it could reach $50 billion by 2029. India, with its biodiversity and traditional knowledge, is well-positioned to capture a significant share of this market. The domestic market for herbal medicine and related products is also substantial, estimated at over $4 billion annually (4).

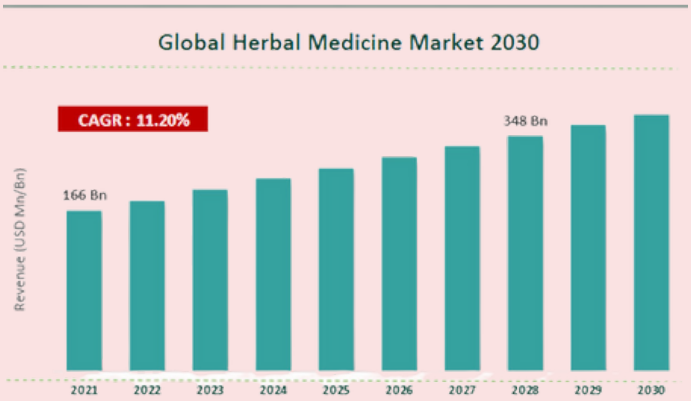

Figure 2. Projected growth of the global phytopharmaceutical market (2020-2030)

4. Opportunities for India in phytopharmaceuticals

4.1. Leveraging biodiversity

India is one of the world's 17 megadiverse countries, home to about 8% of the world's biodiversity. This rich flora includes numerous medicinal plants, many of which have yet to be fully studied for their pharmaceutical potential. The systematic exploration of this biodiversity could lead to the discovery of novel therapeutic compounds (4).

Table 2. Medicinal plant diversity in India's biodiversity hotspots

Biodiversity hotspot	Number of medicinal plant species	Potential therapeutic areas
Western Ghats	3500+	Anticancer, Anti-inflammatory
Himalayas	1700+	Adaptogenic, Cardiovascular
North East India	2000+	Antimicrobial,Antidiabetic
Andaman & Nicobar Islands	1000+	Antiviral,Immunomodulatory

4.2. Integration of traditional knowledge

India's traditional systems of medicine, particularly Ayurveda, offer a wealth of information on the medicinal properties of plants. By integrating this traditional knowledge with modern scientific methods, India can fast-track the discovery and development of new phytopharmaceuticals (4).

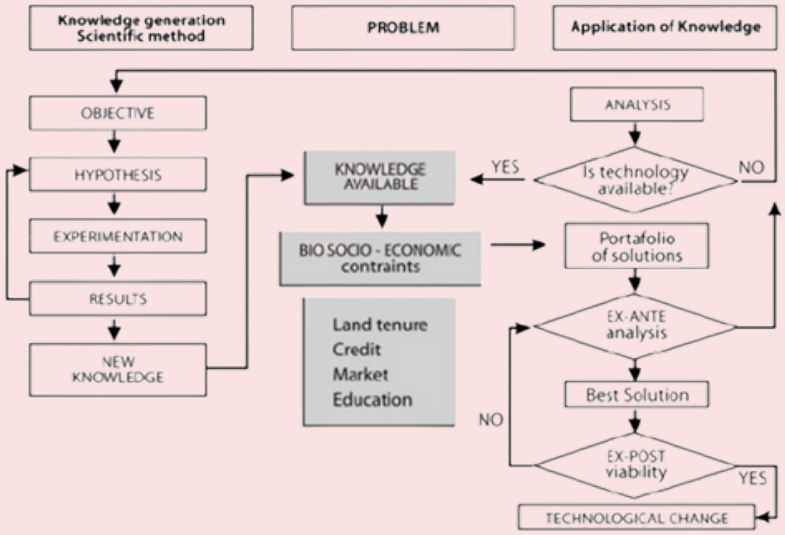

Figure 3. Schematic representation of integrating traditional knowledge with modern scientific methods

4.3. Economic growth and employment

The development of a robust phytopharmaceutical industry in India has the potential to create significant economic value. It could generate employment across various sectors, from agriculture and processing to research and manufacturing. Moreover, it could boost India's pharmaceutical exports, contributing to the country's economic growth (4).

4.4. Healthcare solutions

Phytopharmaceuticals could offer effective and potentially more affordable solutions to various health challenges faced by India's population. These plant-based drugs might be particularly valuable in addressing chronic diseases like diabetes, cardiovascular disorders, and respiratory ailments, which are becoming increasingly prevalent in India (4).

Table 3. Potential phytopharmaceutical solutions for major disease areas

Disease area	Potential phytopharmaceutical solutions	Traditional plant sources
Diabetes	Alpha-glucosidase inhibitors	*Gymnema sylvestre, Pterocarpus marsupium*
Cardiovascular	Antihypertensive agents	*Rauwolfia serpentine, Terminalia arjuna*
Respiratory	Bronchodilators	*Adhatoda vasica, Tylophora indica*
Cancer	Cytotoxic agents	*Catharanthus roseus, Taxus baccata*

4.5. Sustainable development

The cultivation of medicinal plants for phytopharmaceuticals can promote sustainable agriculture practices. It offers an opportunity for farmers to diversify their crops and potentially increase their income. Moreover, it aligns with global trends towards more natural and sustainable products (4).

5. Challenges and considerations

5.1. Quality control and standardization

One of the major challenges in phytopharmaceutical development is ensuring consistent quality and standardization. Plants can vary in their chemical composition based on factors like growing conditions, harvest time, and processing methods. Developing robust quality control measures is crucial for the success of phytopharmaceuticals (4).

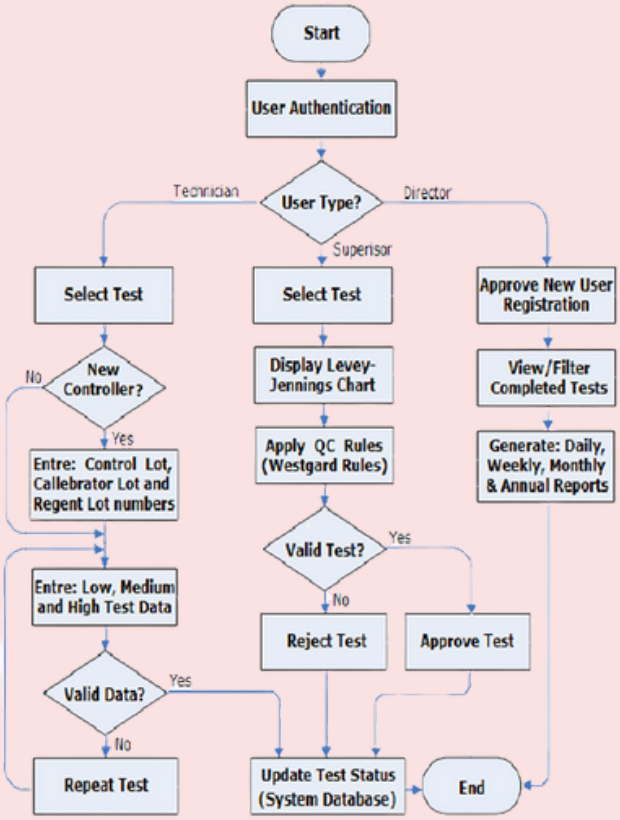

Figure 4. Flowchart of quality control process for phytopharmaceuticals

5.2. Clinical Trials and Efficacy Proof

Demonstrating the efficacy and safety of phytopharmaceuticals through clinical trials can be complex and time-consuming. The multi-component nature of many plant-based drugs poses unique challenges in terms of identifying active ingredients and understanding their mechanisms of action (4).

5.3 Intellectual Property Rights

Protecting intellectual property in phytopharmaceuticals can be challenging, especially when the products are based on traditional knowledge. India needs to navigate the complex landscape of patent laws and traditional knowledge rights to ensure fair benefits to all stakeholders (5).

5.4 Environmental Concerns

As the demand for medicinal plants increases, there's a risk of overexploitation of wild plant populations. Sustainable cultivation and harvesting practices need to be developed and implemented to protect biodiversity (6).

5.5 Regulatory Hurdles

While India has made progress in creating a regulatory framework for phytopharmaceuticals, there's still a need for clearer guidelines and streamlined approval processes. Harmonizing these regulations with international standards is crucial for global market access (6).

6. The path forward: Realizing the potential

6.1. Investment in research and development

To fully capitalize on the potential of phytopharmaceuticals, India needs to significantly increase its investment in R&D. This includes funding for basic research, drug discovery, and clinical trials. Collaboration between academic institutions, research organizations, and the pharmaceutical industry should be encouraged (6).

Table 4. Current and recommended R & D investment in phytopharmaceuticals

R & D Phase	Current investment (% of GDP)	Recommended investment (% of GDP)
Basic research	0.2	0.5
Drug discovery	0.3	0.7
Clinical trials	0.1	0.3

6.2. Capacity building

There's a need to develop a skilled workforce capable of driving innovation in phytopharmaceuticals. This involves enhancing education and training programs in areas like phytochemistry, pharmacognosy, and clinical research (7).

6.3. Policy support

The government can play a crucial role in realizing the potential of phytopharmaceuticals. This could include (7):

- Providing incentives for phytopharmaceutical research and development
- Streamlining regulatory processes
- Supporting the cultivation of medicinal plants
- Promoting India as a global hub for phytopharmaceutical research and manufacturing

6.4. International collaboration

India should seek collaborations with international partners to leverage global expertise and resources. This could involve research partnerships, technology transfer agreements, and joint clinical trials (8).

6.5. Sustainable practices

Developing sustainable cultivation and processing practices for medicinal plants is crucial. This includes promoting organic farming, implementing good agricultural and collection practices (GACP), and establishing fair trade mechanisms to benefit local communities (8).

6.6.Public awareness and acceptance

Efforts should be made to increase public awareness about phytopharmaceuticals. This includes educating healthcare professionals and the general public about the benefits and proper use of these products (8).

7. Conclusion

The field of phytopharmaceuticals presents an immense opportunity for India to leverage its natural resources, traditional knowledge, and scientific capabilities. By developing this sector, India can not only contribute to global healthcare solutions but also drive economic growth, create employment,

and position itself as a leader in this emerging field. However, realizing this potential requires a concerted effort from all stakeholders: government, industry, academia, and local communities. Itdemands a balanced approach that promotes innovation while ensuring sustainability and equitable benefits (9).

As the world increasingly looks towards nature-inspired solutions for health and wellness, India stands at a unique juncture. With its rich biodiversity, ancient wisdom, and growing scientific capabilities, the country has the potential to become a global powerhouse in phytopharmaceuticals. By addressing the challenges and capitalizing on the opportunities, India can unlock the immense potential of phytopharmaceuticals, contributing to both national development and global health. The journey towards this goal will undoubtedly be complex, requiring patience, investment, and collaborative effort. However, the potential rewards in terms of health outcomes, economic benefits, and global leadership make it a journey worth undertaking. As India moves forward in this exciting field, it has the opportunity to write a new chapter in its long history of plant-based healing, one that combines the wisdom of the past with the innovations of the future (10).

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Ginkgo biloba: A review of its pharmacological and therapeutic applications

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Abstract

One of the earliest known medicinal plants, *Ginkgo biloba*, has attracted a lot of interest due to its pharmacological and therapeutic potential in a variety of medical applications. The bioactive elements of *G. biloba,* such as terpenoids, flavonoids, and ginkgolides, are examined in this review along with their various medicinal applications i.e., for neuroprotection, anti-inflammatory, antimicrobial, antioxidant, and anticancer properties. *G. biloba* has been shown in studies to improve memory, lessen neurodegenerative effects, suppress inflammation, fight bacterial resistance, and possibly impede the spread of cancer. Additionally, *G. biloba* has a generally good safety record; though care should be taken to avoid any negative side effects or drug interactions. The potential of *G. biloba* in complementary and alternative medicine is highlighted by the recent developments in nanotechnology, which have improved the bioavailability and effectiveness of its extracts.

Keywords: *Ginkgo biloba*, Polyprenols, Terpenoids, Flavonoids

Abbreviations:
multidrug-resistant Staphylococcus aureus (MRSA)
Ginkgo biloba extract (GBE)
reactive oxygen species (ROS)
superoxide dismutase (SOD)
Alzheimer's disease (AD)
4′–O–methylpyridoxine (MPN)

1. Introduction

It is possible to obtain a number of biologically active organic compounds from medicinal plants. Since time immemorial, there has been a substantial reliance on the curative properties of various plants. Systematic study of these plants yields a broad spectrum of bioactive compounds for the formulation of new medicinal products. Lately, pharmacological studies of a number of plants, used in traditional medicine of various countries have attracted much interest. In the recent past, a great number of traditionally known plants have been studied in detail through scientific approaches and their anticancer, anti-inflammatory, anthelmintic, antibacterial, antifungal, hepatoprotective, antioxidant and larvicidal activities have been established; to name only a few (1).

Taxonomy (1):

Kingdom	Plantae
Subkingdom	Viridiplantae
Infrakingdom	Streptophyta
Superdivision	Embryophyta
Division	Tracheophyta
Subdivision	Spermatophytina
Class	Ginkgoopsida
Subclass	Ginkgoopsida
Order	Ginkgoales
Family	Ginkgoaceae
Genus	Ginkgo
Species	biloba

Ginkgo biloba is also seen as a “living fossil,” one of the oldest seed plants surviving today. This giant tree stands 40-meter tall and shows a life span exceeding one thousand years (2). The word "biloba" comes from the shape of its leaves which has two lobes while "ginkgo" was taken from the Japanese language. The ginkgo tree flourished throughout the Mesozoic era and especially reached the greatest heights in the Jurassic and Cretaceous periods (3). *Ginkgo biloba* is a traditional herbal medicine used in China and other countries for more than 2000 years and it is now being cultivated in Europe, Asia, Argentina, North America and New Zealand (4). *G. biloba* was the earliest plant to grow after the atomic bomb was dropped in Hiroshima, Japan, in 1946. The survival of species is influenced by insects, microorganisms, chemical pollution, and environmental conditions (5). Many diseases, like asthma, TB, skin problems, stomach pain, bronchitis, hearing issues, anxiety, hardening of the arteries, blood clots, heart disease, and diabetes, have been treated with it (4).

2. Active ingredients and their significance

The leaves of *G. biloba* have terpenoids and flavonoids, which are important chemical parts. *G. biloba* includes many other active substances like organic acids, polyprenols, and bioflavonoids. Bilobalide and ginkgolides are two more components of *G. biloba* that are known for their medical uses. There are five kinds of ginkgolides A, B, C, J, and M each with unique features. *G. biloba* has flavonoids as glycoside forms, such as isorhamnetin, kaempferol, and quercetin. A standardized leaf extract of *G. biloba*, called EGb 761, has 10% organic acids, 6% terpenoids, 5%–24% flavonoid glycosides, and other active substances that are known to offer various health benefits (4).

Table 1. Major bioactive components of Ginkgo biloba (4)

Class	Plant parts	Major chemical constituents	Bioactivity
Polyprenols	Leaf	Di-trans-poly-cis-octadecaprenol	Antibacterial properties and safety against the attack by Aβ25-35

Flavonoids	Leaf	Quercetin,kaempferol, isorhamnetin, rutin, luteolin, delphidenon, myricetin	Antioxidation,anticancer, antibacterial, antiviral, anti-inflammatory, and neuroprotective effects
Organic acids	Leaf	Benzoic acid derivatives (ginkgolic acid), N-containing acids	Inhibitory effects on xanthine oxidase (XOD) and antitumor properties
Biflavonoids	Leaf	Sciadopitysin,ginkgetin, isoginkgetin, amentoflavone, bilobetin, 5′-methoxybilobetin	Anti-adipogenesis and anti-obesity properties and significant inhibitory effects on thrombin activity
Terpenoids	Root	Triterpenes: sterols	Protective effects to cerebral hippocampal neurons from epilepsy, antioxidant,anti-inflammatory, antiplatelet, antilipidemic and antiapoptotic properties,enhanced memory and learning abilities, and reduced neuronal damage
	Leaf/root/bark	Sesquiterpene: bilobalide	
	Leaf/root/bark	Diterpenes: ginkgolides M	
	Leaf/root/bark	Diterpenes: ginkgolides A, B, C, and J	
Others	Leaf	Waxes,steroids, 2-hexenal, cardanols, sugars, catechins, proanthocyanidins,phenols, aliphatic acids, rhamnose	Antioxidant,anti-inflammatory, antidiabetic, antiapoptotic, antiradiation, antiviral,antitumor, hepatoprotective, & anti-atherosclerotic

3. Pharmacological actions

3.1. Neuroprotective activity

Most studies on the ginkgo plant's impact on the nervous system mainly used ginkgo leaf extracts and, less often, tablets. These forms helped make blood flow better in the brain's vessels, lower the amount of nerve cells that can get harmed or die, and lessen inflammation in the nervous system. The interventions enhanced memory function, specifically cognitive memory, which is vital for mitigating and diminishing neurodegenerative alterations, especially in Parkinson's and Alzheimer's diseases. Furthermore, these formulations are expected to augment the efficacy of donepezil, a medication traditionally utilized for the treatment of dementia symptoms associated with neurodegenerative conditions (6).

3.2. Anti-inflammatory activity

Laboratory-prepared extracts and their commercial formulations, which incorporated specific constituents such as bilobalide, amentoflavone, ginkgolides (A or B), and water-soluble polysaccharides, were evaluated for their anti-inflammatory efficacy. Each study demonstrated a significant reduction in inflammation. Notably, the most frequently observed decreases in nitric oxide, interferon, prostaglandin E2, TNF-α, IL-1, IL-4, IL-6, IL-12, and IL-1β were recorded in inflammatory tissues (6).

3.3. Anti-microbial activity

It has been observed that ginkgolic acid and *Ginkgo biloba* extract effectively inhibit the formation of bacterial biofilms by *Escherichia coli* O157:H7 and Staphylococcus aureus. Furthermore, our findings indicate that *Ginkgo biloba* exocarp extract can prevent biofilm formation by multidrug-resistant *Staphylococcus aureus* (MRSA) through alterations in the expression of genes associated with biofilm development. One notable coagulase-negative staphylococcus, *Staphylococcus haemolyticus,* is particularly concerning as it tends to infect immunocompromised individuals and is implicated in sepsis, pneumonia, peritonitis, otitis media, and urinary tract infections. The prevalence of resistant strains has increased significantly due to the overuse of antibiotics. The formation of biofilms is a principal mechanism contributing to antibiotic resistance. However, it is important to note that commonly used antibacterial medications in clinical settings are insufficient to prevent the development of *S. haemolyticus* biofilms (7).

3.4. Anti-oxidant activity

Oxidative stress imbalance plays a crucial role in the pathogenesis of Alzheimer's disease (AD). *Ginkgo biloba* extract (GBE) has demonstrated beneficial effects attributed to its ability to scavenge free radicals. Research indicates that GBE can mitigate oxidative damage in cerebellar granule cells and decrease levels of hydrogen peroxide-related reactive oxygen species (ROS) in AD models. Additionally, GBE has been shown to upregulate the expression of antioxidant enzymes and proteins, including superoxide dismutase (SOD) and catalase, in the rat hippocampus and ileum. Furthermore, GBE enhances the activities of glutathione (GSH) reductase and gamma-glutamylcysteinyl synthetase. The primary active compounds responsible for the antioxidant effects of GBE extract are flavonoids, which exhibit properties such as ROS scavenging, elevation of antioxidant proteins, and chelation of prooxidant transitional metal ions. Specifically, flavonoid structures like quercetin and myricetin effectively inhibit the oxidation of tert-butylhydroperoxide. The antioxidant activity of terpene lactones has yet to be thoroughly investigated, likely owing to variations in the types of oxidative stress and the experimental models employed. Additionally, there exists conflicting evidence regarding the superoxide-scavenging capabilities of ginkgolides B, C, J, and bilobalide (8).

3.5. Anti-tumor activity

China has utilized *Ginkgo biloba,* a dioecious species, for cancer treatment for millennia. The seeds consist of the mesosperm, membrane endopleura, and kernel, all enveloped by a fleshy outer layer known as exocarp. Among seed plants, the leaves are characterized by their distinct fan shape, commonly referred to as ginkgo folium. Research has demonstrated the anticancer properties of extracts derived from the seeds, exocarps, kernel, and flowers of *G. biloba (9)*.

3.6. Anti-cancer effect of *G. biloba* seeds

Ginkgo biloba seeds, utilized in traditional Chinese medicine, possess an embryo and nutrient reserves. Studies indicate that they can suppress the proliferation of breast cancer cells by inhibiting the expression of CYP 1B1 (10). Additionally, polysaccharides derived from these seeds have been shown to induce apoptosis in hepatoma cells (9).

3.6.1. Anti-cancer effect of *G. biloba* exocarp extract

The exocarp, or outermost layer of seeds, from *Ginkgo biloba* has been recognized for its anticancer effects. Extracts of the exocarp have been found to enhance the Bax/Bcl-2 ratio, induce apoptosis in Lewis lung carcinoma cells, and impede angiogenesis and metastasis. Additionally, polysaccharides derived from the exocarp have shown therapeutic advantages for cancer patients, including tumor reduction and increased production of ROS. Furthermore, ginkgolic acid (GA), isolated from the exocarp, has been shown to inhibit the invasion, migration, and proliferation of pancreatic cancer cells. Nonetheless, further research is necessary to substantiate the anti-tumor efficacy of GA on healthy cells and to explore its potential application in cancer treatment (9).

3.6.2. Anti-cancer effect of *G. biloba* folium extract

Ginkgo folium has undergone extensive research concerning its anticancer properties, demonstrating

tumor inhibition in the S180 mouse sarcoma model (11). It facilitates caspase-dependent apoptosis across multiple cancer types, such as cervical, colorectal, gastric, and melanoma (9). Despite the occurrence of apoptosis, Ginkgo folium has the capability to impede the cell cycle and suppress the migration and invasion of cancer cells (12). It may also be combined with herbal formulations to demonstrate synergistic effects, such as sensitizing cisplatin-resistant lung cancer cells through the WT1/MVP-mediated stabilization of the mTOR/AKT pathway. Clinical investigations involving EGb761 could elucidate the potential of Ginkgo folium as an adjuvant therapy in cancer treatment (13).

4. Adverse effects

The general conclusion is that *Ginkgo biloba* is safe and well tolerated. Ginkgo extract is recommended to be consumed in the amount of 240 mg a day. Milder adverse effects include headaches, palpitations, upset stomach, diarrhoea, and allergic reactions to the skin. However, several case series noted that the ingestion of ginkgo in the long-term was associated with episodes of bleeding, including cerebral bleeding of a severe nature (14).

5. Toxicity

Ginkgo seeds have been shown to contain cyanogenic glycosides which may be poisonous in nature. Ginkgo seeds have potential toxic effects either upon exposure or when consumed. It may cause potentially serious hypersensitive skin reactions such as acute generalized exanthematous pustulosis (AGEP) and convulsive seizures (14).

Cases of food poisoning due to ginkgo seeds have been established. The most important and primary set of symptoms include all those associated with both tonic and/or clonic seizures; the second being loss of consciousness and vomiting. Ginkgo seed poisoning occurs mainly due to the non-protein neurotoxic agent 4′–O–methylpyridoxine (MPN) which is also referred to as ginkgotoxin and the MPN glucoside that is found in ginkgo seeds. MPN is a type of chemical compound that is found in the vitamin B6 structure and prevents its production, utilization, as well as its activity. The enzymatic activation of vitamin B6 by pyridoxal kinase is also inhibited by MPN. The best way of treating patients who undergo ginkgo seed food poisoning is by vitamin B6. MPN can also be found in ginkgo biloba leaves and in the pulp of ginkgo biloba fruit; however, ginkgo biloba leaves do contain a trace amount of MPN that is not likely to be harmful. Ginkgo absorbent has been shown to enhance the 5-hydroxyomeprazole renal clearance by the CYP2C19 genotype and lessen the hydroxylation effects of omeprazole on the renal portion, thus, there is a high possibility that ginkgo absorbent minimizes the efficacy of drugs containing cytochrome omeprazole 2C19. Ginkgo may cause interactions with these medicines: aspirin, warfarin, trazodone, omeprazole, antihypertensive medications, and antihyperglycemic agents (15). Because of its monoamine oxidase inhibitor-like characteristics, ginkgo can cause serotonin syndrome in patients taking other antidepressants (14).

6. Contraindications

Use of ginkgo should be taken with care by epileptic clients as well as those clients who have tendencies of developing convulsions because ginkgo toxin has been identified to reduce the threshold for seizures. Carrier fleeting toxin is found mainly in seeds but is also present in the ginkgo leaves. Ginkgo should not be used in patients with bleeding disorders or in patient taking NSAIDs, antiplatelet, or anticoagulant therapy. One case reported accidental ingestion of aspirin and ginkgo by an elder person from which he had a tendency to develop spontaneous bleeding in the anterior chamber of the eye iris (14).

7. Advancements and nanotechnology

A significant amount of study has been carried out to prepare metallic nanoparticles employing plant extracts. *G. biloba* is employed as a green reductant for formation of nanoplatelets and anisotropic gold nanospheres. Ginkgo-lactones exhibit low-fat solubility which causes low absorption in the body and an idea to combine nanotechnology to advance the bioavailability and bioabsorption. The antiplatelet aggregation and solubility of ginkgodides including ginkgol including ginkgolide was evaluated and found to be enhanced by ginkgo lactone nanosuspensions (GL-NSs). It has also been postulated that EGb-AgNP has assorted bacteriocidal/fungal and larvicidal properties against the

pathogens such as Salmonella paratyphi, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and so on (16).

8. Conclusion

The ancient medicinal plant *Ginkgo biloba* is recognized for its extensive therapeutic potential, which includes anti-inflammatory, neuroprotective, antimicrobial, antioxidant, and anticancer qualities. Bioactive components called terpenoids, flavonoids, and ginkgolides are found in the plant's leaves, seeds, and other parts. These components have demonstrated exceptional effectiveness in both conventional and alternative medicine. Although the plant is generally safe when taken in accordance with recommended dosages, possible side effects, and interactions—particularly with other medications—must be carefully considered. Although more study is required to maximize its efficacy and safety profiles, *G. biloba's* potential to prevent neurodegenerative diseases and aid cancer treatments is especially encouraging.

Furthermore, new approaches to improving the bioavailability of ginkgo compounds have been made possible by recent developments in nanotechnology, indicating that the combination of *G. biloba* extracts and nanomaterials may greatly increase the therapeutic uses of these plants. As studies go on, *G. biloba's* adaptable bioactivities and inventive potential demonstrate its ongoing significance in creating complementary and alternative treatments for a variety of medical conditions.

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Phytoconstituent based interventions for gastric ulcer management: A review of efficacy and mechanisms

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Abstract
Peptic ulcer is a very common disease of the gastrointestinal system that can cause serious health problems like internal bleeding, perforations and obstruction. In India, it affects about 5 to 10% of the population, particularly men in their fifties. Main cause of peptic ulcers is *H. Pylori* infection and inappropriate use of non-steroidal anti-inflammatory medications. Traditional treatment is becoming ineffective due to the development of resistance in *H.Pylori*. Newer strategies can focus on natural products that are derived from plants. Phytochemicals like alkaloids, flavonoids and saponins present in extracts can promote healing of ulcers by their anti-microbial activity, free radical scavenging effects and anti-inflammatory property.

Keywords: Gastric Ulcer, *H. Pylori*, Phytochemicals

1. Introduction

Gastric ulcer or peptic ulcer disease (PUD) is a very common condition that causes damage to the lining of gastrointestinal tract, resulting in sores larger than 3–5 mm, deep enough to reach the sub mucosa. PUD is estimated to occur in about 5–10% of the population at any time during their lifetime. The disease can cause serious problems, namely, internal bleeding, perforation into the wall of stomach or duodenum, penetration into nearby organs, and obstruction of gastrointestinal tract (1). Approximately 1 in 9 individuals in India, particularly men aged in their fifties, may develop peptic ulcer. About 5,00,00 new patients are diagnosed with peptic ulcer annually (2). Major reasons of PUD are *Helicobacter pylori* (*H. pylori)* infection and inappropriate usage of non-steroidal anti-inflammatory drugs (NSAIDs) (2). Research also indicates that prevalence of PUD is more common in South India compared to North India (2-4).

Time taken off from work, the cost of hospitalization and drugs and requirement of surgeries used to treat PUD is a significant burden on the society leading to significant out-of-pocket expenditures and loss in productivity (5).

2. Pathophysiology and treatment of peptic ulcer disease

Peptic ulcers develop on the walls of the stomach or the duodenum because of an imbalance between aggressive and defensive factors that are present in the gastrointestinal tract. This condition is influenced by the presence of gastric acid, pepsin, and bile which are considered aggressive factors.

In addition *H. pylori* infection also contributes to disruption of the mucosal barrier. The protective mechanisms in the stomach and duodenum include the presence of mucous, prostaglandins and rich supply of blood. Under normal conditions, a healthy gastro-duodenal mucosa maintains an equilibrium between both aggressive and defensive factors. However, when aggressive factors overpower the defensive mechanisms—due to increased acid secretion, *H. pylori* infection, or use of NSAID's—ulcers can develop. The condition may also be exacerbated by other factors such as stress or smoking (6-7).

3. Management of peptic ulcer

Before the discovery of *H. pylori,* it was known that peptic ulcers recurred. The patients were maintained on drugs that suppress acid production like proton pump inhibitors, prostaglandin analogues, and histamine-2 receptor antagonists. These drugs were designed to defend the mucosal lining from damage resulting from gastric acid and promote the healing of existing damage. They formed the first line of treatment and are still prescribed for the treatment of PUD (8). These medications have several side effects and studies indicate the development of antibiotic resistance in *H. pylori*. New strategies for managing the challenging *H. Pylori* infection are the need of the hour. Natural products, from medicinal plants, are being explored as potential sources because of their diverse chemical structures (9,10). They can serve as complementary treatments alongside conventional therapies for PUD. Extensive research conducted on various plant-derived compounds has shown protective effects against gastric ulcers through multiple mechanisms.

4. Phytoconstituents with anti-ulcer activity

Several medicinal plants containing phytochemicals that belong to flavonoids, alkaloids, saponins, terpenes, and polyphenols can help in mitigating the symptoms of peptic ulcers. Many of these phytochemicals have antibacterial activity against *H. pylori*. Table 1 gives a list of a few phytochemicals that have a protective role in the management of PUD.

Table 1. Few Phytochemicals with protective effect in peptic ulcer disease

S. No.	Phytochemical	Class	Source	Effect	Ref
1	Eucalyptol or 1,8-Cineole	Monoterpene	Eucalyptus oil	Gastroprotective and healing effect	7
2	Limonene	Monoterpene	*Artemisia dracunculus L* (tarragon)	Cytoprotective action	7
3	Curcumin	Alkaloid	*Curcuma longa* (turmeric)	Reducion the pro inflammatory cytokines TNF-α, IL-1β, IL-6, IL-8	9
4	Berberine	Alkaloid	*Berberis L.*(Barberry)	Increased expression of eNOS mRNA and inhibited expression of iNOS mRNA.	14
5	Quercetin	Polyphenols	*Momordica cymbalaria Hook f* (Little Wild Gourd)	Decreased gastric acidity through anti-apoptotic mechanisms	11,12
6	Kaempferol-3-O-rutinoside	Polyphenols	*Foeneculum vulgare* (Fennel)	Reduction in the activity of lipid peroxidation and amplification of the antioxidant activity	15,17
7	Glycyrrhizin	Sapponins	*Glycyrrhiza glabra* (Licorice)	Protective role against acid and pepsin secretions by covering the site of lesion and promoting the mucous secretion	18

4.1.Flavonoids (Quercetin, Rutin)

Flavonoids are natural anti-inflammatory and antioxidant agents. This property helps in reducing inflammation in the gastric mucosa and provides protection against oxidative stress. The antioxidant effect is helpful in scavenging free radicals, contributing to the healing of damaged tissues and inhibiting the progression of ulcers. Studies have proposed the role of flavonoids from *Momordica cymbalaria* in promoting wound healing in the gastric mucosa. Aqueous extract of *M. cymbalaria* fruits significantly decreases total acidity and ulcer index in experimental models. The presence of flavonoids, particularly quercetin in *M. cymbalaria,* is believed to contribute to ulcer healing. This effect can be ascribed to reduction in oxidative stress which in turn enhances mucosal protection. Histopathological analyses show a marked reduction in gastric lesions and improvements in mucosal integrity in groups treated with aqueous extract of *M. cymbalaria*. The results endorse the traditional use of this plant in the management of PUD (11,12).

4.2. Alkaloids (Berberine)

It has been known for many years that many alkaloids possess antimicrobial and anti-inflammatory effects. Berberine mitigates the inflammatory processes associated with PUD. It enhances the formation of nitric oxide and improves the endothelial function. Nitric oxide is responsible for causing vasodilation and reducing the ulcerogenic risk factors (13). Berberine can decrease the expression of inducible nitric oxide synthase (iNOS), which is responsible for increased production of free radicals that cause cytotoxicity. By decreasing iNOS expression, berberine helps maintain a more stable NO level, which is beneficial for the protection of gastric mucosa and healing of gastric ulcers (14).

4.3. Polyphenols (Tannins, Catechins)

Polyphenols, including tannins and catechins, are are responsible for scavenging free radicals and reducing oxidative stress in the gastrointestinal tract. Polyphenols can inhibit inflammatory cytokines, contributing to the prevention and treatment of ulcers. *Zingiber officinale*, *Foeniculum vulgare* and *Curcuma longa* are some plants that are rich in polyphenols and can be potentially used in the mitigation of PUD due to their anti-inflammatory, antioxidant, antimicrobial, and cytoprotective properties (15,16). The ulcer preventive effects of ginger, fennel and turmeric have been investigated in various studies, particularly focusing on their efficacy in experimental models in rats. This activity in part has been attributed to the reduction in the activity of lipid peroxidation and amplification of the antioxidant activity (17).

4.4. Saponins (Glycyrrhizin)

Several studies have been carried out highlighting the role of licorice in the treatment of PUD. A double-blind study involving 40 patients with confirmed peptic ulcers evaluated the efficacy of a quadruple therapy regimen consisting of amoxicillin, metronidazole, omeprazole, and bismuth sub nitrate compared to a similar regimen where licorice replaced bismuth. After one month of treatment, endoscopic evaluations showed that the treatment with licorice extract was similar to that seen with bismuth. Thus, it was concluded that licorice offers a low-cost and well tolerated treatment with minimal side-effects (18). The healing effect of licorice was because of the rise in concentration of prostaglandins in the digestive tract that led to promotion of secretion of mucus in the stomach.

5. Conclusion

The causes of peptic ulcer disease (PUD) are diverse and complex, requiring targeted therapies to effectively manage and reduce complications. PUD being one of the most prevalent gastrointestinal disorder, poses a significant global health concern due to its high morbidity and mortality rates. Preclinical studies have substantiated the anti-ulcer potential of phytochemicals present in plants and their extracts, however, to confirm the efficacy and safety of their use in patients' further clinical trials are necessary. Standardization of plant based medications and the regulations governing them is a big lacuna for ensuring the quality, safety, and effectiveness of these products. Development of guidelines for stringent quality control and ensuring good manufacturing processes will enhance confidence of the consumer in using herbal remedies. Additionally, incorporating plant-based products into dietary practices or as supplements may complement traditional treatment approaches for PUD.

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Women's health: Harnessing the chemo-preventive potential of phytochemicals for breast cancer


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Abstract
Breast cancer continues to be one of the most prevalent forms of cancer, morbidity and mortality in women globally, with increasing incidence rates projected to surpass 3 million new cases annually by 2040. Current treatment modalities, including surgery, radiation, and chemotherapy, often face limitations such as drug resistance, significant side effects, and poor outcomes for metastatic cases. This highlights the urgent need for effective prevention and treatment strategies. Phytochemicals compounds naturally present in fruits, vegetable and medicinal plants exhibit promising anticancer properties, influencing key biological processes such as cellular proliferation, apoptosis, and metastasis. This review explores the chemo preventive potential of various phytochemicals, including polyphenols, flavonoids, carotenoids, and terpenoids, emphasizing their mechanisms of action and molecular targets relevant to breast cancer. The safety, low toxicity, and accessibility of these compounds position them as viable complementary or alternative options for breast chemoprevention and therapy.

Keywords: Breast cancer, Chemoprevention, Phytochemicals

1. Introduction

Despite significant medical advancements, breast carcinoma remains the second most occurring and lethal cancer impacting women. Over the past four decades, the prevalence of breast cancer has risen dramatically. Around 2.3 million new cases were reported worldwide in 2020, resulting in around 685,000 deaths, with marked geographic differences across various countries and regions. Notably, high-income countries account for a larger share of breast cancer fatalities. Projections indicate that by 2040, there will be over 3 million new cases of breast carcinoma are expected, resulting in more than 1 million mortalities each year (1).

Breast cancer is classified based on the presence of hormone receptors estrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor positive (HER2+), and triple-negative (TNBC), which lacks these receptors. The estrogen receptor (ER) is crucial for diagnosis, as about 70–75% of invasive breast cancers have high ER levels. The progesterone receptor (PR) is found in over 50% of ER-positive patients but is rare in ER-negative cases. PR levels are influenced by ER, indicating a functioning ER pathway. Both ER and PR are commonly found in breast cancer cells and serve as important diagnostic and prognostic markers. HER2 is expressed in about 15–25% of breast cancers (2).

Breast cancer treatments currently include surgical options, radiation therapy, hormone therapy, targeted therapy, immunotherapy, and various chemotherapy drugs such as paclitaxel, doxorubicin, cisplatin, docetaxel, carboplatin, epirubicin, bevacizumab, and cyclophosphamide (3). Nevertheless, these treatments have several limitations, including drug resistance, disease progression, unnecessary exposure of healthy tissues, and a poor prognosis for metastatic breast cancer. Additionally, the significant side effects linked to these therapies have significantly decreased their effectiveness (4,5).

2. Anticancer properties of phytochemicals

An urgent demand exists for developing efficient strategies in the management of breast cancer therapy that has prompted to explore various natural substances as potential supplementary or alternative cancer therapies. Many nature-derived compounds, particularly phytochemicals, have demonstrated anticancer effects by impacting the onset, progression and tumour advancement. They achieve this by regulating numerous mechanisms, such as cell growth, differentiation, programmed cell death, and metastasis. Many cancer treatments currently approved are derived from phytochemicals or their structural analogues, with several of these compounds presently undergoing clinical studies (4,5).

Various phytochemicals have been thoroughly studied for their antitumor properties including examination of safety, minimal toxicity, and wide accessibility contributing to their appeal in cancer research as depicted below (6).

Table 1. Reported phytochemicals in the chemoprevention of breast cancer

S.No.	Phyto-chemicals	Source	Reported anti-cancer activity in breast cancer	Ref
1	Curcumin	*Curcuma longa,* Zingiberaceae (Turmeric)	Curcumin contributes to arrest breast cancer (BC) cells in the cell cycle and notably triggers programmed cell death (apoptosis) in these cells	(7)
2	Resveratrol	*Vitis vinifera,* Vitaceae (Grapes)	The anticancer actions of resveratrol in breast cancer involve the suppression of cell proliferation	(8)
3	Carnosic acid	*Salvia officinalis* L., Lamiaceae (Sage)	Carnosic acid strongly suppresses the development of ER-negative human breast cancer cells	(9)
4	Quercetin	*Punica granatum,* Lythraceae (Promegranate)	The study reported that quercetin can induced G2/M phase arrest in MDA-MB-453 cells lines	(10)
5	Apigenin	*Psidium guajava*, Myrtaceae (Guava)	Apigenin induced programmed cell death; cell cycle halt; suppression of fatty acid synthase (FASN)	(11)
6	Tangeretin	Citrus peels, Rutaceae (Orange)	The antiproliferative effect of Tangerin associated with cell cycle arrest at the G1 phase	(12)

7	Genistein	Glycine max, Fabaceae (Soyabean)	Genistein target the estrogen receptor (ER) human epidermal growth factor receptor-2 (HER2)	(13)
8	Cyanidin	Prunus genus, Rosaceae (Cherries)	Cyanidin inhibit breast cancer cell migration and invasion	(14)
9	Silibinin	*Silybum marianum,* Asteraceae (Milk Thistle)	Silibinin affects both estrogen receptors (ER), α and β; prevents metastasis by inhibiting EMT	(15)
10	Urosilic acid	*Ocimum basilicum,* Lamiaceae (Basil)	Ursolic acid induce G1 cell cycle arrest and promoted mitochondrial-induced programmed cell death in breast cancer cells	(16)
11	Limonene	*Citrus limon,* Rutaceae (Lemon)	Limonin Suppress metastasis in breast cancer via a cyclin D1-dependent pathway	(17)
12	Psoralidin	*Psoralea corylifolia,* Leguminosae (Bemchi)	Psoralidin primarily exerts its anticancer effects by blocking tumor cell growth and triggering apoptosis	(18)
13	Ellagic acid	*Rubus idaeus,* Rosaceae (raspberry)	Ellagic acid Activates of the p53 tumor suppressor pathway; leading to cell cycle arrest	(19)
14	Paclitaxel	*Taxus brevifolia* Taxaceae (Taxol)	Paclitaxel disrupts the dynamics of microtubules and their polymerization, hindering mitosis progression by causing failures in chromosomal segregation, ultimately leading to apoptosis induction and mitotic arrest	(20)

ER-negative: Estrogen receptor negative, EMT: Epithelial–mesenchymal transition, p53: Tumor protein, BC-Breast cancer

3. Future prospects for phytochemical use in breast cancer management

To minimize adverse reactions, there is a potential to combine phytochemicals with approved chemotherapeutic drugs, potentially leveraging nanotechnology approach to improve delivery and reduced toxicity. Encouraging further research into the molecular mechanisms of these compounds, along with initiating clinical trials, is vital to better understand their interactions with current therapies and to validate their efficacy and safety. Additionally, raising public awareness about the cancer-preventive benefits of phytochemicals and educating healthcare professionals on their integration into patient care plans is essential for broader acceptance and application.

4. Conclusion

In conclusion, cancer development is a complex process with multiple influencing factors. The intervention with phytochemicals, whether used alone or in combination, may yield positive effects on cancer chemoprevention. With the identification of several molecular targets for many of these compounds, we can anticipate effective prevention by adopting novel treatment strategies.

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Bioactive compounds: Integrating nature's weapon for combating the antimicrobial resistance


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Abstract

The rise of antibiotic resistance has motivated researchers to search for new antimicrobial agents. About 7.7 million deaths are associated with bacterial infections each year, of these 4.95 million are due to drug-resistant bacteria, and 1.27 million are caused by resistance to current antibiotics. Bioactive secondary metabolites have antibacterial, anti-inflammatory, antifungal, and anti-cancer properties, with several modes of antibacterial action including inhibition of efflux pump, disruption of the cell wall, alteration of the permeability of membrane, inhibition of replication and translational machinery. In addition to natural plant products phyto-derived nanomaterials have emerged as a powerful tool against bacterial biofilms. These nanomaterials can penetrate biofilm barriers and target bacterial cells directly. This article explores the potent bioactive metabolites with their effective antimicrobial activity against multidrug-resistant pathogens and the advancement of nanotechnology for delivering phyto-based drugs combating anti-microbial resistance.

Keywords: Bioactive compounds, Secondary metabolites, Anti-microbial resistance, Efflux pump, Multidrug resistance.

1. Introduction

The widespread use of antibiotics has led to the emergence of antimicrobial resistance (AMR), which has a detrimental effect on human health. AMR has become a serious scientific concern, prompting research into phyto-based products as powerful and promising antibacterial compounds. Traditional medicinal plants are receiving a lot of attention because of their phytochemical significance and ability to combat diseases that are resistant to antibiotics effectively. Pharmacognosy, which involves the identification and evaluation of bioactive chemicals as a substitute source in the treatment of microbial infections, was the focus of the scientific community. The majority of poor nations use phytoconstituents as traditional medicine. Bioactive secondary metabolites have antibacterial, anti-inflammatory, antifungal, and anti-cancer activity. This type of compound shows promise in the therapy of human microbial illness conditions.

Terpenes, phenolics, nitrogen-containing, and sulphur-containing metabolites are the four groups into which the bioactive secondary metabolites are divided. The Methylerythritol Phosphate (MEP) and Mevalonate pathways are the two main pathways used to synthesise the five isoprene units that form terpenes. These terpenes exhibit their antimicrobial activity against both Gram-positive and Gram-negative multidrug-resistant bacteria as it inhibits the potent efflux pump (1). Terpenes rupture the cell membrane and inhibit the transcription and the translational machinery. The broad-spectrum antimicrobial activity, especially antibacterial, has been reported in the phenolics (tannin), as it kills the bacteria by disrupting the cell membrane, inhibiting cell wall biosynthesis, and fatty acid biosynthetic pathways (2). The classification of the bioactive secondary metabolite and its mode of action is shown in Figure 1.

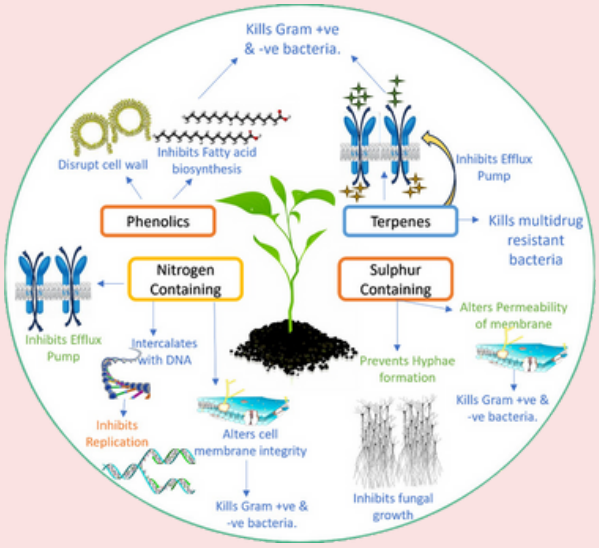

Figure 1. Classification of the bioactive secondary metabolites and its mode of action

The sulphur-containing bioactive compound, i.e., glucosinolates, exerts the apoptotic activity and inhibits the hyphal growth. Defensin belongs to sulphur-containing secondary metabolites that kill gram-positive and gram-negative bacteria by altering the permeability of the cell membrane.

The nitrogen-containing compound, including michellamine b, works effectively against HIV (retrovirus) by inhibiting its protein activity (3). The alkaloids, including reserpine, exert their antimicrobial activity by inhibiting the efflux pump, Berberine intercalates with DNA and inhibits replication, and Evodiamine alters the cell membrane integrity.

The bioactive compounds (chrysoeriol, luteolin, isorhamnetin glycoside, and flavonol) work against both gram-positive and gram-negative bacteria, i.e., *Staphylococcus aureus* and *Vibrio cholerae* via degradation of the intracellular content and disruption in the plasma membrane.

2. Bioactive metabolites with potent antimicrobial activity

Several phyto-based essential oils from *Verbenaceae* and *Lamiaceae* exhibit anti-quorum sensing and antibiofilm properties against multidrug-resistant bacteria. A list of potent bioactive metabolites approved by WHO against antibiotic-resistant bacteria with their minimum inhibitory concentration (MIC) is listed in Table 1.

Table 1. List of potent bioactive metabolites approved by WHO against antibiotic-resistant bacteria

Potent plant with extract part	Bioactive Compounds	MIC	Antibiotic-resistant bacteria	Ref
Curcuma longa (Rhizome)	Chitosan	1024µg/ml	*P. aeruginosa* resistant against carbapenem	(4)
Avicennia marina (Leaf)	Phenolics,Terpene(triterpene),Flavonoids, Glycosides	4.0mg/ml	*E. faecalis* resistant against the Vancomycin	(5)
Andrographis paniculate (Leaf)	Saponins	25mg/ml	*A. baumannii* resistant against carbapenem.	(6)
Laureliopsis philippiana (Leaf)	Eudesmol, Eucalyptol, Isohomogenol	64µg/ml	*H. pylori*	(7)
Thymus vulgaris	Monoterpenes, Sesquiterpenes, Diterpenes	512µg/ml	*S. aureus, H. influenzae*	(8)

Moringa oleifera (Seed)	Phenolics, Flavonoids	0.5µg/ml	*H. pylori*	(9)
Illicium verum (Seed)	Flavonoids	0.25-1 µg/ml	MRSA	(10)
Matayba oppositifolia (Bark)	Palimitic acid	250-1000 µg/ml	*A. baumannii, P. aeruginosa, Enterobacter* resistant against carbapenem,	(11)
Stryphnodendron adstringens (Bark)	Tannin, Polyphenols	12.5mg/ml, 3.12mg/ml, 0.78mg/ml	*K. pneumoniae,* MRSA, *S. pneumoniae.*	(12)
Acacia Senegal (Leaf)	Phenolics, Flavonoid	256µg/ml	Multidrug resistant *E. coli, K. pneumoniae.*	(13)

3. Synergistic effect of bioactive compounds combating the antimicrobial-resistant bacteria

Nowadays, antibiotic-resistant properties have become the most challenging and emerging problem, which leads to a serious challenge for pharmaceutical companies to develop new drugs. To overcome the side effects of synthetic medicine nowadays, the researchers are mainly focusing on the area of natural products with fewer side effects and multitargets. There are some multidrug-resistant pathogens *(Enterococcus faecium, Staphylococcus aureus, Acinetobacter baumannii, and Enterobacter species)* to which WHO has given priority for searching new antibacterial agents (14). Several in vitro studies have demonstrated that the combination of the plant extract with antibiotics dramatically reduced the minimum inhibitory concentration. Potent bioactive metabolites combined with currently available antibiotics can kill both gram-positive and gram-negative bacteria by blocking the formation of their cell walls' proteins (15). Numerous plant extracts, such as those from leaves, stems, and roots, contain bioactive chemicals and have inhibitory effects against the different pathogens depicted in Figure 2.

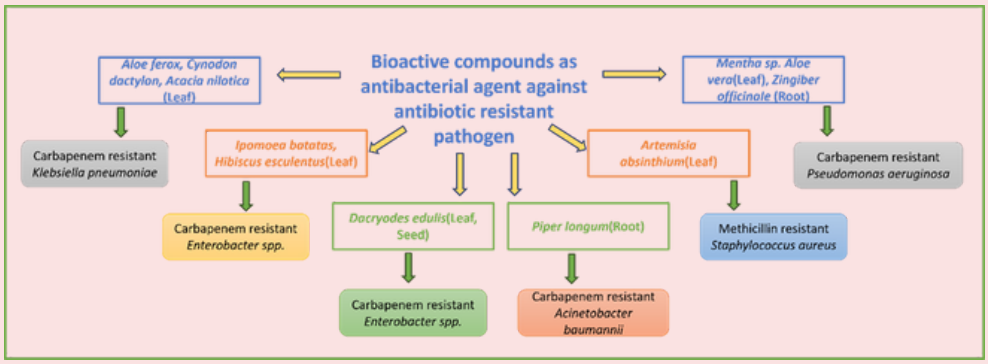

Figure 2. Natural extracts containing bioactive compounds as antibacterial agents against antibiotic-resistant pathogens.

Combinatorial effects resulting from interactions amongst the bioactive metabolites are the medicinal plant's distinctive property. One of the examples is illustrated here. Propolis exhibits the best antimicrobial activity and is comprised of three types of flavonoids (Chrysin, Galangin, and Pinocembrin), which work against the nine pathogens when combined with other additives (16).

- Pinocembrin, when combined with chrysin, leads to a less fractional inhibitory concentration (FIC) index of 0.57 for *S. aureus*, 0.76 for L. monocytogenes, 1.12 for E. *coli*, 1.00 for *K. pneumoniae*, 0.82 for *P. aeruginosa*, 1.23 for *C. albicans*, 1.00 for *C. neoformans,* and 1.13 for *C. tropicalis.*
- Pinocembrin when combined with galangin leads to 1.10 (FIC) for *S. aureus*, 0.19 for *L. monocytogenes,* 1.00 for *E. faecalis*, 0.63 for *E. coli*, 1.00 for *K. pneumoniae*, 0.52 for *P. aeruginosa*, 0.74 for *C. albicans*, 0.40 for *C. neoformans,* and 0.44 for *C. tropicalis.*

- Chrysin combined with the galangin leads to the 0.75 (FIC) index for *S. aureus*, 0.26 for *L.* monocytogenes, 0.81 for *E. faecalis,* 0.65 for *E. coli*, 1.00 for *K. pneumoniae,* 0.49 for *P. aeruginosa*, 1.00 for *C. albicans*, 1.00 for *C. neoformans,* and 0.14 for *C. tropicalis*.
- Out of all the possible combinations, pinocembrin with galangin exhibits a synergistic interaction against the *L. monocytogenes C. neoformans* and *C. tropicalis*. While the chrysin galangin exhibits a synergistic interaction against the L. monocytogenes, *P. aeruginosa,* and *C. tropicalis* (16).

4. Nanotechnology-based phytochemical drug delivery system

Nanotechnology is the most potent technique to overcome the drawbacks in the delivery of the drug due to its stability and bioactivity, and it prevents the degradation of the phytochemicals. There are some nano-based biocompatible formulations which include, nanoliposomes, micelles, nanoemulsions, and nanostructured lipid carriers which increase the entrapment capacity, stability and solubility of the phyto-compounds (17).

- **Liposomes:** A spherical vesicle containing the structure of a lipid bilayer consisting of phospholipid and cholesterol. These liposomes (400nm-2.5µm) nanoparticles can carry both hydrophobic and hydrophilic drugs as shown in Figure 3. Food and Drug Administration has agreed and approved the liposome-carrying drugs in the market. Nanoliposomes consist of nano-sized liposomes with large surface area encapsulated compounds.

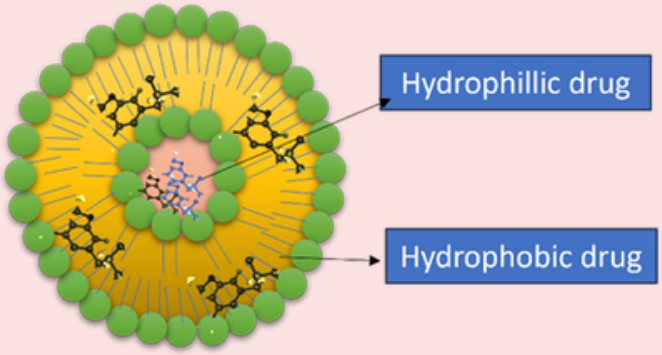

Figure 3. Liposomes carrying phyto-based drug

- **Nanoemulsions:** Nanoemulsions are used to enhance the solubility, stability of the hydrophobic plant-based compounds for their better absorption efficiency and bioavailability.
- **Micelles:** Micelles consist of 10 to 100 nm spherical colloids made up of amphiphilic monomers and polymers (18). Surfactants are generally used in the preparation of the micelles. Micelles generally increase the bioavailability, reduce the toxicity, and exhibit the absorption level (18). These polymeric micelles have a higher capacity to load the phyto-based drugs and are more stable as compared with the liposomes (19).
- **PLGA Nanoparticles:** Poly lactic-coglycolic acid after the hydrolysis inside the body produces the lactic acid and glycolic acid. PLGA reduces toxicity, and it can deliver bioactive compounds such as carvacrol, saponins and menthol.

5. Success stories in plant-based antibacterial activity

The phyto-based formulation is the holistic approach to evade multidrug-resistant bacteria. Various bioactive metabolites worked successfully as antibacterial agents against both antibiotic-resistant and sensitive bacteria. Based on the *in vitro* and *in vivo* studies, the bioactive compound beta-sitosterol works effectively against pulmonary tuberculosis and it helps in the proliferation of the peripheral blood lymphocytes by the huge production of the interferon-gamma and interleukin-2 (20). The better efficiency of beta-sitosterol leads to alternative treatment for tuberculosis.

Acinetobacter baumannii is an effective human pathogen as it causes the loss of skin grafts, slow healing of wounds, bioactive compounds eugenol and transcinamaldehyde reduces the adherence of the *A. baumannii* and invasion to the human keratinocytes. The RT-qPCR resulted a reduction in the transcription of the genes associated with the development of the *A. baumannii* biofilms. This study implies that the combination or individual treatment of eugenol and transcinamaldehyde both might be utilized against the *A. baumannii* infections (21).

Ahmed et.al (22) reported the efficacy of the flavonolignan silymarin in the treatment of hepatitis. Silymarin is composed of a combination of flavonolignans extracted from *Silybum marianum*. Silybin was reported as a most potent antiretroviral agent. Alpha-viniferin, another bioactive compound exhibits antioxidant, antitumor, anticancer, and anti-arthritis activity and also inhibits acetylcholinesterase, prostaglandin, and cyclooxygenase enzymatic activity. It showed excellent efficiency against the three resistant strains methicillin susceptible *S. aureus*, methicillin-resistant *S. aureus*, methicillin resistant *S. epidermidis*. Alpha-vinifera was effective against *S. aureus* confirmed by the RT-qPCR (23).

Plantago lanceolata was reported as an effective medicinal plant in the treatment of dental caries caused by *Streptococcus* and *Lactobacillus*. Plantago contains a high amount of phenolics i.e. flavonoids and tannin, which prevent bacterial growth, and tooth decay and reduce the proliferation and virulence of pathogenic flora (24).

6. Conclusion

Phytochemicals are the most effective way to deal with the growing number of AMR propensity. Since phyto-based bioactive chemicals are inexpensive, effective, and easy to use, they might be the greatest substitute for antibiotics. In the treatment of microbial disorders, phyto-based bioactive chemicals are effective and promising options due to their broad-spectrum specificity and multitargeted methods. There are some challenges in the use of phytomedicine as there is low aqueous solubility, less permeability across the intestinal epithelial cells, minimum therapeutic uses and rapid elimination hence, to overcome these challenges, nano-phytomedicine is the best technology for controlled release which increases the efficacy of phytomedicine, increases the entrapment capacity, releases onto the target site reduces the toxicity, and increases the solubility and synergistically active when combined with existing synthetic antibiotics (25).

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Current insights on nutritional deficits from junk food and their risk of early puberty and PCOS in females



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Abstract

High junk food consumption, low in essential nutrients, contributes to hormonal imbalances and metabolic issues that increase the risk of early puberty and Polycystic Ovary Syndrome (PCOS) in young females. Junk foods' unhealthy fats, sugars, and additives can lead to insulin resistance, obesity, and hormonal shifts, elevating PCOS risk, which affects between 3.7% and 22.5% of teenage girls and young women in India. Early puberty, now affecting about 10.4% of Indian children, is also linked to obesity and junk food intake. Addressing these risks through balanced nutrition, lifestyle changes, and education is essential. New anti-obesity drugs and nutritional counseling offer promising interventions to support hormonal health and prevent these conditions in adolescent girls. This newsletter underscores the importance of diet in hormonal development and reproductive health.

Keywords: Junk Food, Polycystic Ovary Syndrome, Obesity, Early Puberty

1. Introduction

Nutritional deficiencies can arise from junk food consumption (high levels of saturated fats, trans-fatty acids, and refined sugar), which may ultimately contribute to the development of Polycystic Ovary Syndrome (PCOS) due to its high calorie and low nutrient content. These junk foods are often rich in sugars, unhealthy fats, and additives but lack essential vitamins, minerals, and fibers. Regularly replacing nutritious meals with junk food can result in inadequate intake of vital nutrients, leading to conditions like infertility, early puberty, and PCOS in females resulting in cervical carcinoma (1). The global consumption of junk food is a widespread issue, with over 70% of people incorporating it into their diets were shown in Figure 1. This trend poses significant public health concerns, particularly among young adults. Research shows that women with PCOS are at risk of deficiencies in essential minerals like potassium and magnesium, as well as vitamins B12 and B9. Vitamin D deficiency is also associated with PCOS, depression, and insulin resistance. Maintaining a healthy body mass index (BMI) is crucial for regular menstrual cycles. Therefore, encouraging adolescent girls to adopt a balanced and nutrient-rich diet is vital for supporting a healthy menstrual cycle and sustaining a normal BMI. Numerous research has looked into the possibility that eating junk food can cause irregular menstruation (2). This newsletter aims to raise awareness among women and adults about the link between junk food consumption, PCOS, and early puberty syndrome. It provides nutritional approaches to help prevent PCOS and delay early puberty in females.

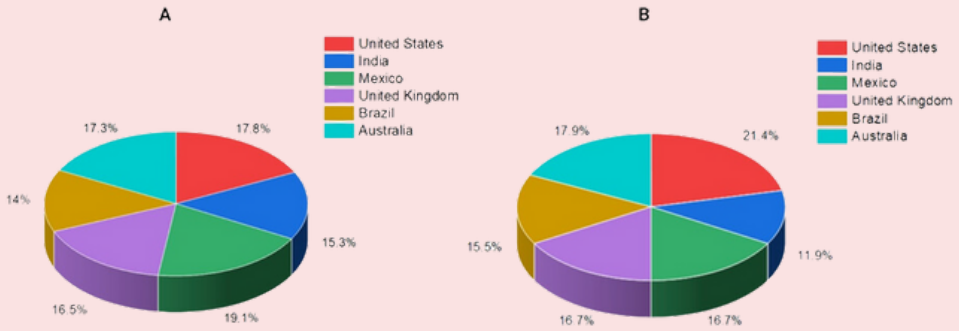

Figure 1. A) shows that in 2024, junk food consumption is high globally, with Mexico at the top (75%) followed by the U.S. (70%), Australia (68%), the U.K. (65%), India (60%), and Brazil (55%) (3). This widespread trend raises health concerns due to poor nutrition;

B) highlights obesity prevalence across the same countries, with the U.S. highest at 36.2%, followed by Australia (30.4%), Mexico (28.9%), the U.K. (28.0%), Brazil (26.8%), and India (20.5%). The data underscores the global impact of obesity, often linked to diet, lifestyle, and socioeconomic factors (4).

2. Junk food and PCOS

As of 2024, the prevalence rate of PCOS in India is a growing concern, with studies estimating that between 3.7% to 22.5% of Indian women of reproductive age are affected (5). Teenagers are the most vulnerable. PCOS is classified to be an oligogenic condition with a combination of hereditary and environmental factors that affect how the condition manifests in PCOS women in a variety of clinical and biochemical ways. Diet, way of life, and physical exercise all have an impact on the health of women (6). Women with PCOS often have elevated LH/FSH ratios and exhibit symptoms like anovulation, hyperandrogenism (e.g., hirsutism, acne, alopecia), and polycystic ovaries. Common complications include insulin resistance, weight gain, cardiovascular diseases, infertility, and pregnancy-related issues like miscarriage and gestational diabetes. A significant percentage (38-88%) of women with PCOS are overweight or obese, and a modest weight loss (5%) can notably improve symptoms (7). Obesity exacerbates PCOS symptoms, particularly hyperandrogenism, and is linked to junk food consumption. PCOS often runs in families and is considered a genetic condition with a peri-pubertal onset (8).

3. Junk food and early puberty

As of 2023, the prevalence of early puberty in India has been rising, with approximately 10.4% of children, particularly between the ages of 8 and 13, showing signs of early puberty (9). The consumption of junk food is increasingly being linked to the early onset of puberty in children. Junk foods, typically high in unhealthy fats, sugars, and artificial additives, contribute to rapid weight gain and obesity, which are significant risk factors for early puberty (10). These foods cause hormonal imbalances by influencing insulin levels and the release of sex hormones like estrogen. Excessive intake of such foods can lead to increased body fat, which affects leptin levels a hormone closely associated with the timing of puberty. Studies indicate that early puberty is linked to both physical and psychological challenges, including increased risk of obesity, type 2 diabetes, cardiovascular issues, and emotional stress. Early exposure to adult hormone levels also affects children's mental health, potentially leading to low self-esteem and increased rates of depression. Addressing junk food consumption is thus crucial for promoting healthy development and delaying the onset of puberty (11).

4. Junk food and obesity

Obesity, characterized by excessive body fat deposition, significantly increases the risk of various health issues. Body mass index (BMI), determined by weight, height, and age, is used to identify

obesity-related metabolic disorders. A high BMI is closely linked to women's metabolic processes and gynaecological issues, such as PCOS, abnormal uterine bleeding, infertility, and pregnancy failure. Obesity is a major public health challenge, with projections suggesting that by 2030, 55 to 60 percent of today's youth will be obese (12). In women with PCOS, excess androgens can lead to increased fat levels and appetite regulation issues, including dysregulated ghrelin and reduced cholecystokinin synthesis. This relationship highlights the serious health concerns associated with obesity and its co-morbidities, especially as lifespans increase. Junk food, high in unhealthy fats and sugars, contributes to weight gain and obesity, which disrupts hormone balance and promotes inflammation, increasing the risk of ovarian cancer in women is shown in Figure 2. Menstrual abnormalities, PCOS, and infertility are among the reproductive problems that obese women face.

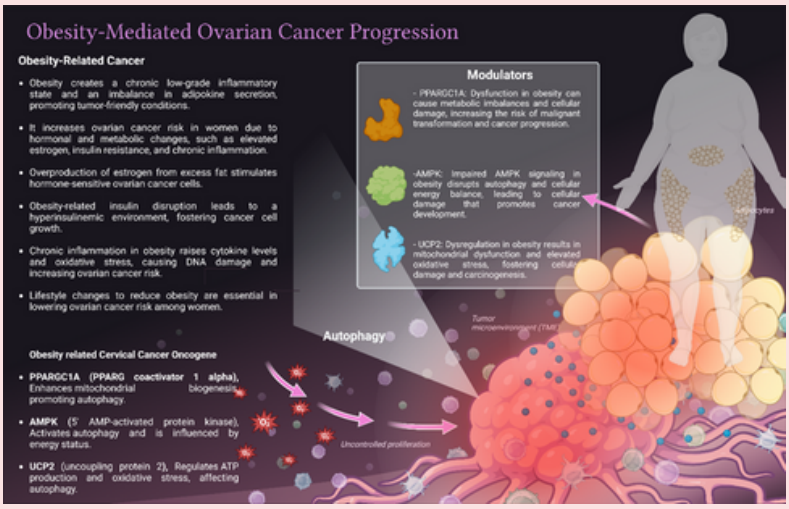

Figure 2. Obesity raises ovarian cancer risk, with nearly 15% of female cancer cases linked to obesity. It disrupts estrogen and insulin levels, causing chronic inflammation. Lifestyle changes are essential to lowering this risk, and a new drug targeting obesity-related ovarian cancer offers a promising treatment.

5. Strategies to overcome junk food and their risk of early puberty and PCOS in females

To address the impact of junk food on early puberty and PCOS in females, it's essential to focus on balanced nutrition, lifestyle changes, and awareness. Junk food, laden with unhealthy fats, sugars, and additives, contributes to weight gain, insulin resistance, and hormonal imbalances, all of which can accelerate puberty and increase the risk of PCOS in young females (13). Junk food-related physiological effects are shown in figure 3. Here are some strategies to counteract these effects:

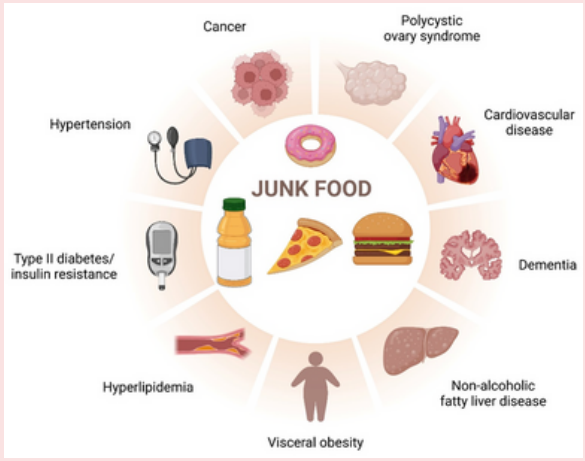

Figure 3. The figure shows health conditions and risks linked to lifestyle choices, especially poor diet and junk food consumption. It connects these habits to cancer, PCOS, hypertension, cardiovascular disease, type II diabetes, dementia, hyperlipidemia, and non-alcoholic fatty liver disease, emphasizing how junk food and obesity drive metabolic and chronic health issues.

Encouraging nutrient-dense diets rich in whole foods fruits, vegetables, whole grains, lean proteins, and healthy fats can support balanced hormonal growth and stabilize blood sugar levels, helping reduce risks of early puberty and PCOS. Limiting processed and sugary foods can prevent weight gain and insulin resistance, which are linked to these conditions; instead, healthier snacks like fruits, nuts, and yogurt are recommended. Regular physical activity, such as walking or cycling, maintains healthy weight, regulates hormones, and reduces stress. Education on the impact of junk food on hormonal health can motivate healthier choices among young females and parents. For those already experiencing early puberty or PCOS symptoms, professional support from healthcare providers and nutrition counselling can aid in managing these issues. Recent advancements in anti-obesity and nutritional drugs also offer potential solutions for addressing nutrient deficits tied to junk food, early puberty, and PCOS (14).

6. New drug discoveries

Novo Nordisk has introduced a new obesity pill named amycretin, which has shown greater efficacy than the existing drug Wegovy in early clinical trials. This medication targets the GLP-1 hormone, similar to other weight loss treatments, and may provide a faster rate of weight loss while maintaining a safe side effect profile comparable to that of Wegovy and Ozempic. In preliminary phase 1 trials, participants taking amycretin lost up to 13.1% of their body weight in just three months, indicating its potential as a significant advancement in obesity treatment (15).

Zepbound, a dual GIP/GLP-1 agonist approved in late 2023, has shown substantial weight loss, averaging 21% during clinical studies. Administered weekly, it effectively helps individuals with obesity and reduces the risk of developing type 2 diabetes from pre-diabetes (16). Semaglutide also plays a key role in managing obesity and cardiovascular risks. Nutritional recommendations for patients using these medications emphasize a balanced intake of whole grains, fruits, and vegetables while limiting sugars and saturated fats, with a target fiber intake of 21–25 grams per day for women. For adolescents with PCOS, Medical Nutrition Therapy focuses on personalized dietary interventions to improve insulin resistance and reproductive health, while metformin shows promise in managing early puberty and related weight issues (17).

7. Conclusion

Junk food, high in unhealthy fats and sugars and lacking essential nutrients, is linked to early puberty and PCOS in females. This diet causes nutritional deficiencies, weight gain, and insulin resistance, disrupting hormonal balance and exacerbating PCOS symptoms, particularly due to obesity. Adopting a balanced, nutrient-rich diet and promoting nutritional education among adolescents and parents are essential preventive measures. Emerging anti-obesity treatments and personalized dietary guidance offer support, but prevention remains key for better reproductive and metabolic health.

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Formulation and standardization of phytopharmaceuticals: A Veterinary perspective

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Abstract

Phytopharmaceuticals, or plant-derived therapeutic products, have historically played a key role in veterinary medicine, offering natural treatment options for various animal health concerns, including inflammation, infection, and immune support. Despite the modern shift towards synthetic drugs, renewed interest in sustainable and natural remedies has spurred research and regulatory support from bodies like the EMA and FDA. This article explores the formulation and standardization processes crucial for integrating phytopharmaceuticals into veterinary practice, covering extraction techniques, dosage forms, excipient choices, and quality control measures to ensure consistent efficacy and safety. Additionally, it highlights historical influences, current demand trends, and challenges in standardizing these plant-based products, aiming to provide a structured approach to phytopharmaceutical use in general veterinary care.

Keywords: Veterinary Medicine, Formulation, Standardization, Animal Health

1. Introduction

Phytopharmaceuticals, defined as plant-derived products with therapeutic intent, have been utilized in veterinary medicine for centuries (1). They are effective for a wide range of animal health issues, including anti-inflammatory, antimicrobial, antiparasitic, immunomodulatory, and antioxidative effects. Their unique active compounds such as alkaloids, flavonoids, tannins, and essential oils provide diverse pharmacological actions beneficial for managing common veterinary conditions.

Along with lower incidence of side effects, regulatory support from various authorities (like European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA)) have bolstered further research and approvals in this area. Continued research and clinical trials further support the adoption of phytopharmaceuticals, paving the way for their integration into standard veterinary protocols. Thus, scientific validation is boosting the credibility and availability of phytopharmaceuticals in veterinary medicine.

The growing interest in natural remedies, coupled with concerns regarding synthetic pharmaceuticals, has spurred research into the area of herbal medicines for animals. The formulation and standardization of these products are critical to their successful integration into veterinary practice, ensuring that they meet the necessary standards for safety and efficacy.

2. Historical context of phytopharmaceuticals in veterinary medicine

Phytopharmaceuticals have deep historical roots in veterinary medicine, tracing back thousands of years when ancient civilizations used plant-based remedies to treat animal ailments (2).

2.1. **Ancient traditions:** Early societies like the Egyptians, Indians, and Chinese extensively used plants for animal care. Ancient Egyptian texts reference garlic for livestock infections, Ayurveda in India employed turmeric and neem, and Traditional Chinese Medicine used herbs like astragalus to boost animal immunity.

2.2. **Medieval documentation**: During the Middle Ages, herbal knowledge expanded, with European and Islamic texts detailing plant treatments for livestock. European compendiums like *The Herbal of Dioscorides and works* by Islamic scholars spread herbal knowledge across regions.

2.3. **Renaissance and veterinary schools**: Veterinary medicine became formalized in the 18th century, but traditional herbal practices remained especially in rural settings. Texts like *The Modern Farrier* integrated herbal remedies with emerging veterinary practices.

2.4. **Industrial shift to synthetic drugs:** The Industrial Revolution brought synthetic drugs, and herbal medicine use declined. However, rural areas retained plant-based knowledge, using herbs where synthetic options weren't accessible.

2.5. **Modern revival and research**: The 20th century saw a revival of interest in natural therapies due to concerns over drug side effects and antibiotic resistance. Research validated plant compounds like curcumin (turmeric) for inflammation, sparking consumer demand for natural veterinary options.

2.6. **Current recognition and regulation:** Today, with advancements in standardization, phytopharmaceuticals are recognized as valuable therapeutic options. Regulatory bodies like the EMA have begun approving certain herbal veterinary drugs, supported by ongoing research on safety and efficacy.

3. Formulation development

The development of phytopharmaceuticals involves several critical steps, including extraction methods, dosage form selection, excipient incorporation, and quality control measures.

3.1.Extraction methods: The extraction process is pivotal in isolating active ingredients from plant materials. Various techniques are employed, including:

- **Maceration:** Soaking plant material in a solvent to extract soluble compounds, typically done at room temperature for an extended period.
- **Percolation:** Involves the gradual passage of a solvent through plant material, resulting in a concentrated extract with higher potency.
- **Distillation:** A method mainly used for volatile compounds, where steam distillation extracts essential oils from plant materials.
- **Supercritical fluid extraction (SFE):** Utilizes supercritical CO2 as a solvent, offering an efficient and environmentally friendly method for extracting a wide range of phytochemicals.
- **Ultrasonic extraction:** Enhances the extraction efficiency using ultrasonic waves, leading to higher yields of active compounds.

The choice of extraction method significantly influences the concentration and bioavailability of the active ingredients in the final product (3).

3.2. Dosage forms

The formulation can take various dosage forms, each selected based on the target species and therapeutic intent:

- **Liquid Extracts**: Highly concentrated solutions that are often administered directly or mixed with food.
- **Powders**: Dried and ground herbal materials that can be encapsulated or incorporated into animal feed.
- **Tinctures:** Alcohol-based extracts that provide potent concentrations of active constituents, suitable for precise dosing.
- **Tablets and Capsules:** Solid dosage forms that allow for accurate dosing and are convenient for long-term administration.

- **Topical Preparations:** Creams, gels, and ointments designed for local application, particularly for skin conditions.

3.3. Excipients

Excipients play a crucial role in enhancing the stability, bioavailability, and palatability of phytopharmaceutical formulations. Common excipients include:

- **Binders**: Substances like starch or cellulose that help hold the formulation together, particularly in tablet formulations.
- **Fillers**: Agents such as lactose or microcrystalline cellulose that add bulk to formulations, facilitating easier dosing.
- **Preservatives**: Added to prevent microbial growth and extend shelf life, with natural options preferred in herbal products.
- **Flavoring agents**: Used to improve palatability, especially for oral formulations, making them more acceptable to animals.
- **Thickeners:** Agents like xanthan gum or guar gum that enhance the viscosity and stability of liquid formulations.

3.4. Quality control

Quality control measures are critical to ensuring that the formulated product is safe, effective, and consistent. Key components include:

- **Physical and chemical testing:** Assessing properties such as pH, viscosity, and solubility to ensure they meet specified standards.
- **Microbiological testing**: Evaluating the formulation for the presence of pathogens or spoilage organisms, ensuring safety for animal use.
- **Stability studies:** Conducting tests to determine how the formulation performs over time under various environmental conditions (e.g. temperature, humidity) to establish shelf life.
- **Packaging considerations:** Selecting appropriate packaging materials that protect against environmental factors and contamination, ensuring product integrity.

4. Standardization

Standardization is essential for ensuring the consistent quality and therapeutic efficacy of phytopharmaceuticals in veterinary medicine (4). This process begins with phytochemical profiling, which identifies and quantifies active plant compounds. Techniques like High-Performance Liquid Chromatography (HPLC) separate and measure specific compounds, Gas Chromatography (GC) is used to analyze volatile compounds, and Mass Spectrometry (MS) provides detailed molecular characterization, enhancing our understanding of pharmacologically active ingredients.

To further ensure quality, establishing robust standards is critical. Monographs define essential attributes such as identity, purity, potency, and safety thresholds providing reference standards for both manufacturers and regulators, while acceptable limits control contaminants like heavy metals, pesticides, and microbial load. Regulatory compliance is maintained through guidelines set by authorities such as the World Health Organization (WHO), European Medicines Agency (EMA), and U.S. Food and Drug Administration (FDA), which enforce safety and labelling requirements to meet safety and efficacy benchmarks in veterinary settings (5).

Finally, ensuring batch-to-batch consistency is key to maintaining therapeutic reliability. This involves controlled cultivation for quality raw material sourcing, Good Manufacturing Practices (GMP) during production to limit variability, and comprehensive documentation of sourcing, extraction methods, and testing outcomes, all of which help trace and address any inconsistencies in quality across different batches. Together, these measures form a robust framework that supports the safe, effective, and standardized use of phytopharmaceuticals in animal health care (4,5).

5. Efficacy and safety

The efficacy and safety of phytopharmaceuticals in veterinary medicine are foundational, requiring thorough evaluations throughout their development and use.

Clinical trials are essential, with well-designed, randomized, and controlled studies that utilize sufficient sample sizes to generate reliable data on therapeutic effects. Trials focus on assessing clinical outcomes, such as symptom relief, recovery rates, and improvements in animals' overall health, while also rigorously monitoring for any adverse effects, ensuring that the benefits outweigh potential risks.

Toxicity studies further inform safety by evaluating different exposure types: acute toxicity studies assess immediate reactions to high doses to determine the median lethal dose (LD50), while chronic toxicity studies examine long-term effects, identifying any cumulative risks from prolonged use. Reproductive and developmental toxicity studies are also vital for breeding animals, ensuring that phytopharmaceuticals are safe for pregnant or lactating animals and do not negatively impact offspring.

Additionally, drug interaction studies are crucial for safe co-administration with conventional veterinary medications. Pharmacokinetic interactions examine how phytopharmaceuticals affect the absorption, distribution, metabolism, or excretion of other drugs, while pharmacodynamic interactions determine whether the plant-based drugs enhance or inhibit the effects of conventional treatments. This layered approach to assessing efficacy, toxicity, and interactions provides a robust framework for the safe and effective integration of phytopharmaceuticals into veterinary care (6).

6. Market trends and challenges

The demand for phytopharmaceuticals in veterinary medicine is growing rapidly, driven by an increased preference for holistic care among animal owners who favor natural remedies, leading more veterinarians to integrate phytotherapy into their practices. This trend aligns with global shifts toward sustainability and the use of natural ingredients in health care, fostering broader acceptance of phytopharmaceuticals.

However, standardization faces significant challenges. Variability in raw materials influenced by environmental conditions, cultivation methods, and harvesting practices leads to inconsistencies in active compounds, impacting product reliability. Additionally, a lack of extensive research limits robust data on the safety and efficacy of many herbal products, further complicating their standardization.

Finally, regulatory hurdles present difficulties, as manufacturers must navigate complex, often fragmented regulatory frameworks, affecting the availability and accessibility of phytopharmaceuticals in the veterinary market. These factors highlight the need for more comprehensive research, streamlined regulations, and improved quality control to meet the rising demand effectively.

7. Future prospects and conclusion

Phytopharmaceuticals hold significant promise for enhancing veterinary care through their therapeutic potential and natural origins. However, rigorous formulation and standardization processes are critical to ensuring the safety, efficacy, and quality of these products. By establishing stringent quality control measures and adhering to regulatory guidelines, veterinary practitioners can confidently incorporate phytopharmaceuticals into their treatment protocols, ultimately improving animal health and welfare. Further, more species and disease specific approaches need to be adopted in fostering the use of phytopharmaceuticals alongside conventional therapies in veterinary domain. This will further solidify the role of phytopharmaceuticals in veterinary medicine, offering effective, safe, and natural alternatives for the care of animals.

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Harnessing the power of phytopharmaceuticals in chronic disease management: Prevention and treatment

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Abstract

Globally, chronic illnesses like cancer, diabetes, and cardiovascular disease are becoming the biggest health burdens. Despite their effectiveness, conventional therapy approaches frequently have serious side effects and are not always suitable for long-term care. Because of their promise to offer safer and more efficient chronic illness care, natural alternatives specifically, phytopharmaceuticals have gained attention. Bioactive substances derived from plants, known as phytopharmaceuticals, provide a variety of pharmacological advantages, such as immunomodulatory, antioxidant, and anti-inflammatory qualities. The mechanisms of action, instances of particular phytochemicals, and difficulties in bringing these compounds to clinical usage are the main topics of this review, which looks at the function of phytopharmaceuticals in the prevention and treatment of chronic diseases.

Keywords: Phytopharmaceuticals, Chronic Disease, Alkaloids, Flavonoids, Polyphenols, Diabetes, Cardiovascular Disease

1. Introduction

Chronic diseases such as cardiovascular disease, diabetes, cancer, and neurodegenerative disorders pose a substantial health burden worldwide. The World Health Organization (WHO) reports that non-communicable diseases (NCDs) are the cause of more than 70% of deaths worldwide. Among these, cardiovascular diseases stand out, making up almost 31% of all deaths (1). While Pharmaceutical drugs have greatly improved the treatment of these illnesses, limitations like side effects, drug resistance, and limited effectiveness in halting disease progression have prompted scientists to explore natural alternatives. Phytopharmaceuticals, which are bioactive compounds obtained from plants, are increasingly being recognized as promising tools for preventing and treating chronic diseases. They provide a wide range of therapeutic advantages while causing fewer side effects (2). Phytopharmaceuticals focus on various pathways and biological processes such as oxidative stress, inflammation, and immune modulation. These are crucial factors in the development of chronic diseases. By impacting these pathways, phytopharmaceuticals both prevent the onset of disease and enhance disease management, leading to an improved quality of life for those affected.

2. Mechanism of action of phytopharmaceuticals

Phytopharmaceuticals work by engaging in a range of mechanisms crucial for preventing and managing chronic diseases. These mechanisms consist of antioxidant activity, anti-inflammatory effects, immunomodulation, and regulation of lipid and glucose metabolism.

2.1. Antioxidant activity

Oxidative stress, caused by an imbalance between free radicals and antioxidants, plays a crucial role in the onset and advancement of chronic conditions such as cardiovascular disease, diabetes, and cancer. Phytochemicals such as flavonoids, polyphenols, and carotenoids have powerful antioxidant properties. They work by scavenging free radicals and reducing oxidative stress. For instance, curcumin, extracted from turmeric, exhibits strong antioxidant properties, safeguarding against cellular harm linked to neurodegenerative conditions and specific types of cancer (3,4). Antioxidants work to neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS), two culprits involved in cell damage and the onset of chronic inflammation. By bolstering cellular antioxidant defenses, phytopharmaceuticals have the potential to postpone the development of chronic illnesses or decelerate their advancement. This can lessen the strain on healthcare systems and enhance patient results.

2.2. Anti-inflammatory effect

Chronic inflammation is widely recognized as a major contributor to various chronic conditions such as cardiovascular disease, diabetes, and arthritis. Inflammation is controlled by a variety of pro-inflammatory cytokines and enzymes, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Phytochemicals such as resveratrol, found in grapes, and quercetin, a flavonoid found in apples and onions, regulate these inflammatory pathways by inhibiting pro-inflammatory mediators. The anti-inflammatory effects can be especially advantageous in the prevention and management of diseases characterized by inflammation, such as cardiovascular disease and arthritis (5). Curcumin, a phytochemical known for its anti-inflammatory properties, has displayed promise in reducing the activity of nuclear factor kappa B (NF-κB), a transcription factor that controls the production of different inflammatory cytokines. Engaging in such activity renders curcumin an appealing therapeutic option for inflammatory conditions; nonetheless, bioavailability hurdles persist.

2.3. Immunomodulation

Immunomodulatory properties of phytopharmaceuticals assist in boosting the immune system's capacity to combat infections, cancer, and various chronic ailments. Ginsenosides from ginseng are known to enhance immune responses, thus aiding the body's defense against abnormal cell growth linked to cancer (6). Phytochemicals, such as echinacea, have a long history of traditional use due to their immune-boosting properties. Studies suggest that they could improve both humoral and cellular immunity. These compounds can be especially helpful in preventing infections that worsen chronic disease symptoms or advance disease progression.

2.4. Regulation of lipid and glucose metabolism

Several phytochemicals, like berberine and epigallocatechin gallate (EGCG) found in green tea, possess beneficial effects on lipid and glucose metabolism. These properties make them valuable tools in the management of metabolic disorders, including diabetes and obesity. Berberine, for example, triggers AMP-activated protein kinase (AMPK) which is a vital controller of glucose and lipid metabolism. This action enhances insulin sensitivity and decreases blood lipid levels (7). Aside from berberine, green tea catechins have also been proven to reduce LDL cholesterol and body weight, enhancing metabolic well-being. Phytopharmaceuticals possess qualities that make them an appealing choice for addressing metabolic syndrome, a group of conditions that elevate the chances of developing cardiovascular disease and diabetes.

3. Phytopharmaceuticals in managing specific chronic diseases

3.1. Cardiovascular disease

Cardiovascular diseases (CVDs) are the primary cause of death worldwide, resulting in millions of fatalities each year.Phytopharmaceuticals such as omega-3 fatty acids, resveratrol, and garlic extract have proven to have beneficial effects on the heart, such as lowering blood pressure, enhancing endothelial function, and reducing cholesterol levels. Omega-3 fatty acids, which are abundant in flaxseed and fish oil, have been shown to effectively lower triglyceride levels and enhance cardiovascular well-being (8).

Resveratrol, a polyphenol present in grapes, is linked to enhanced vascular function and lower cardiovascular disease (CVD) risk due to its anti-inflammatory and antioxidant qualities. Garlic extract, which contains sulfur compounds such as allicin, has demonstrated promise in lowering blood pressure and enhancing cholesterol levels, providing a supplementary option to traditional cardiovascular disease therapies (9).

3.2. Diabetes and metabolic syndrome

The prevalence of diabetes and metabolic syndrome has increased significantly in recent decades, influenced by lifestyle changes and dietary habits. Phytopharmaceuticals like curcumin, berberine, and green tea catechins have been researched for their ability to control glucose metabolism and enhance insulin sensitivity. Curcumin, specifically, boosts insulin signaling pathways, assisting in the regulation of blood glucose levels (10). Berberine has demonstrated its ability to enhance lipid profiles and lower fasting blood glucose levels, establishing it as a beneficial phytochemical for managing diabetes. In addition to that, green tea catechins help diminish oxidative stress and inflammation. This plays a vital role in improving the handling of metabolic syndrome and its related risks (11).

3.3. Cancer prevention and management

Cancer is a major global threat, characterized by intricate mechanisms that encompass various molecular and cellular processes. Phytopharmaceuticals are showing great promise for both cancer prevention and treatment, thanks to their ability to target multiple mechanisms. For instance, EGCG, a polyphenol present in green tea, has demonstrated the ability to hinder tumor growth through triggering apoptosis and obstructing angiogenesis (12). Sulforaphane, a compound discovered in broccoli, demonstrates anti-carcinogenic characteristics as it affects phase II detoxification enzymes and triggers cell cycle arrest in cancer cells. These compounds, when used alongside traditional chemotherapy, can have synergistic effects, possibly enhancing treatment results with reduced side effects (13).

3.4. Neurodegenerative disease

The increase in neurodegenerative conditions such as Alzheimer's and Parkinson's has led researchers to investigate the neuroprotective benefits of phytopharmaceuticals. Curcumin, resveratrol, and ginkgo biloba extracts demonstrate potential in reducing oxidative stress, by inhibiting beta-amyloid plaque formation, and improving cognitive function (14). Resveratrol, in particular, has been examined for its potential to activate sirtuins, which are proteins responsible for cellular stress response and aging. These mechanisms hint at the possibility of phytopharmaceuticals contributing to the delay of onset and progression of neurodegenerative diseases, providing a natural method for maintaining cognitive health (15).

3.5. Respiratory disease

The management of diseases related to the respiratory system has recently developed much interest in the use of phytopharmaceuticals with their diverse bioactive constituents, having both anti-inflammatory and bronchodilatory effects. Anti-bacterial properties do also help in improving lung functions with respiratory symptoms by using plants like *Glycyrrhiza glabra*, liquorice; *Adhatoda vasica,* vasaaka; *Zingiber officinale*, ginger; and *Curcuma longa*, turmeric. *Glycyrrhiza glabra* has anti-inflammatory actions that inhibit pro-inflammatory cytokines, useful in treating chronic obstructive pulmonary disease and asthma (16). *Adhatoda vasica* contains vasicine, a bronchodilator and expectorant that reduces mucus formation, being beneficial in the treatment of chronic bronchitis (17). In addition, *Zingiber officinale* possesses very potent anti-inflammatory and antioxidant activities, and it reduces airway hyper reactivity and symptoms of asthma (18). *Curcuma longa* contains curcumin, which has been widely known for its broad spectrum of anti-inflammatory activity against allergy and inflammatory responses in respiratory diseases (19). A number of phytopharmaceuticals possess fewer side effects than drugs and can be used as adjunct treatments to improve the effectiveness of therapy and adherence in patients.

4. Challenges in the development of phytopharmaceuticals

Although their potential is promising, various obstacles must be overcome for them to establish as

conventional therapeutic

4.1.Bioavailability and absorption

One significant drawback of phytopharmaceuticals is their limited bioavailability, potentially impeding their therapeutic effectiveness. One example would be curcumin, which has limited absorption and quick metabolism, leading to minimal overall effectiveness. Various strategies, including nanoencapsulation and combining with bioenhancers such as piperine, have been researched to enhance the bioavailability of phytochemicals, thereby boosting their efficacy in clinical applications (20).

4.2. Standardization and quality control

Phytopharmaceuticals tend to exhibit variations in their chemical composition because of distinctions in plant species, geographical sources, and extraction techniques. The variability involved makes standardization more complex, thereby posing a challenge in guaranteeing consistent effectiveness and safety. Advances in extraction and quality control techniques are essential to address these challenges, facilitating the development of dependable phytopharmaceutical formulations (21).

4.3. Clinical evidence and regulatory challenges

Despite promising results in preclinical studies on phytopharmaceuticals, there exists a notable gap in robust clinical evidence. Large-scale, randomized clinical trials are crucial for determining the effectiveness and safety of phytopharmaceuticals in the management of chronic diseases. Moreover, the regulatory frameworks for phytopharmaceuticals differ greatly between countries, posing a challenge in obtaining approval for clinical applications. In contrast to traditional medications that undergo thorough testing via established regulatory procedures, phytopharmaceuticals frequently encounter varying levels of regulation. In numerous regions, they are classified as supplements instead of drugs. This implies that they might not have to undergo rigorous efficacy and safety testing requirements. The absence of consistent regulatory oversight impacts both consumer confidence and the capacity of healthcare providers to confidently endorse phytopharmaceuticals (22).

5. Future directions in phytopharmaceuticals research

As interest in this field grows, various avenues in research and development show promise in improving the effectiveness of these compounds in managing chronic diseases:

5.1. Advancement in drug delivery system

One of the most promising approaches to enhance the effectiveness of phytopharmaceuticals involves the creation of innovative drug delivery systems. Nanotechnology-based delivery methods, such as liposomes, nanoparticles, and micelles, have the ability to improve the bioavailability and stability of phytochemicals. These delivery systems protect phytochemicals from deterioration in the gastrointestinal tract and enhance their absorption in specific tissues. For example, nano-encapsulated curcumin has demonstrated increased stability and bioavailability, resulting in improved effectiveness in animal models of cancer and neurodegenerative diseases (23).

Moreover, crafting specialized delivery mechanisms to precisely target phytochemicals towards affected tissues can minimize adverse reactions and enhance treatment effectiveness. These specialized methods hold particular value in the field of cancer treatment. Precise targeting minimizes harm to healthy cells while amplifying the anti-cancer properties of phytopharmaceuticals.

5.2.Exploring synergistic combinations

When phytochemicals are combined with conventional pharmaceuticals or other phytochemicals, they can create synergistic effects that improve therapeutic results. Studies have indicated that when curcumin is combined with anti-inflammatory medications such as non-steroidal

anti-inflammatory drugs (NSAIDs), it can improve pain relief and decrease the necessary dosage of the standard drug, thereby reducing unwanted side effects (24). In a similar vein, the pairing of resveratrol with chemotherapeutic drugs has been shown to enhance the effectiveness of cancer treatment and decrease toxicity (25). Researching the pharmacodynamics and pharmacokinetics of such combinations could lead to the development of more effective, multi-targeted therapies that capitalize on the advantages of both synthetic drugs and natural compounds.

5.3. Phytochemical genomics and precision medicines

Phytochemical genomics is an up-and-coming area of study that delves into the impact of genetic factors on how individuals react to phytochemicals. This has the potential to tailor phytopharmaceutical treatments to each person's unique needs. Understanding individual genetic profiles could aid in identifying patients more likely to benefit from specific phytochemicals, ultimately optimizing therapeutic outcomes. Certain genetic variations can influence the body's metabolism or response to substances like resveratrol or curcumin, which can impact their effectiveness in preventing and treating diseases (26).

Incorporating precision medicine into phytopharmaceutical research has the potential to enhance treatment approaches by making them more tailored and personalized. This can ultimately improve patient outcomes and decrease the likelihood of adverse effects.

5.4. Integrating the wealth of traditional and modern medical knowledge

Traditional medicinal practices, including Ayurveda, Traditional Chinese Medicine (TCM), and Indigenous wisdom, have a history of utilizing medicinal plants for managing chronic health conditions. Modern phytopharmaceutical research can benefit immensely by merging traditional knowledge with scientific methods. This integration helps in pinpointing plants and compounds with a proven historical efficacy. Integrative approaches can speed up the discovery of potential therapeutic compounds, all the while aligning traditional knowledge with scientific principles (27).

Moreover, partnering with traditional healers and ethnobotanists has the potential to enrich phytopharmaceutical studies by bringing to light plant species and preparation techniques that could be easily disregarded in contemporary pharmacological research. Phytopharmaceuticals present an intriguing and largely unexplored potential for the prevention and management of chronic illnesses.

6.Conclusion

Phytochemicals offer a valuable complement or alternative to conventional therapies with their multi-targeted mechanisms of action. These include antioxidant, anti-inflammatory, immunomodulatory, and metabolic-regulating effects. However, certain challenges like inadequate bioavailability, absence of standardization, and limited clinical evidence are currently impeding their extensive utilization in clinical settings. Advancements in drug delivery systems, standardization methods, and personalized approaches can overcome these obstacles, paving the path for enhanced and available phytopharmaceutical solutions. Additionally, it is crucial to blend traditional knowledge with meticulous clinical trials and implement clear regulatory frameworks. These steps are essential for advancing the safe and efficient utilization of phytopharmaceuticals in managing chronic diseases. Research is ongoing, and it is becoming more apparent that phytopharmaceuticals hold promise in enhancing the health outcomes of patients with chronic diseases.

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A review on *Ehretia laevis*: A potential medicinal herb

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Abstract

For years, medicinal plants have served as the foundation of traditional medicine, providing a wealth of bioactive chemicals with potential therapeutic applications. The purpose of this review is to thoroughly investigate the medicinal properties, phytochemical profile and traditional uses of *Ehretia laevis*. Plants like *Ehretia laevis* have been shown in scientific studies to be effective in treating various diseases including inflammation, oxidative stress, cancer and neurological problems, as it contains chemical constituents like flavonoids (Quercetin, Kaempferol), alkaloids (Ehretine, Ehretinine) saponins (Oleanolic acid, Ursolic acid) etc. These chemical constituents are obtained from the Ehretia laevis plant extract with different extraction methods. It emphasizes the promise of plants as a source of new drugs and also highlights current research limitations. This review provides a platform for future research into the development of botanical therapies.

Keywords: Phytochemical Profile, Traditional Medicine, Therapeutic Applications

1. Introduction

Plants are known in the pharmaceutical industry for their great structural diversity and spectrum of medicinal activities. Phytochemicals are biologically active molecules found in plants that are produced from various plant parts including leaves, flowers, seeds, bark and roots. Plants used in traditional medicine contain a diverse spectrum of phytochemicals and are used to treat acute, chronic and infectious diseases. *Ehretia laevis*, a tribal herb found in Maharashtra's Wardha region, has been proven to be highly effective in wound healing (1).

2. Plant profile

Ehretia laevis is a rare Indian herb in the medicinal industry due to its extensive therapeutic properties. It belongs to the Boraginaceae or Borage family. *Ehretia laevis* is a very valuable medicinal plant which is becoming rare in Maharashtra. It has sacred significance among Hindus (2).

(a) (b) (c)

Figure 1. (a) Flowers; (b) Leaves; (c) Tree of Ehretia laevis (2,3,5)

2.1. Morphology

Ehretia laevis is a medium-sized tree with dark green leaves ranging from 2-7.8 cm in length and 1.2 to 3.8 cm in width. The plant has obtuse leaves with 5-7 lateral veins and short 2-3 cm, and its bark is uneven and light grey. *Ehretia laevis* flowers and fruits, which bloom from January to April, are white and can reach up to 8 mm in size (4).

2.2.Taxonomical classification

Table 1. Taxonomic hierarchy of *Ehretia laevis*

Kingdom	Plantae
Division	Tracheophyta
Class	Magnoliopsida
Order	Boraginales
Faminly	Boraginaceae
Genus	Ehretia
Species	Laevis
Botanical Name	*Ehretia laevis* (Roxb)

Table 2. Synonyms of *Ehretia laevis*

English	Ehretia
Hindi	Bhairi, Chamror,Datranga, Tamoriya
Gujarati	Vadhavaradi
Konkan	Datingal
Marathi	Datrang, Ajaanvruksha
Telugu	Tellajuvvi, Paldattam
Tamil	Kuruviccai, Kalvirasu

2.3. Geographical distribution

Ehretia laevis is primarily grown in India, Australia, Pakistan, Africa, Bhutan, Vietnam, Sri Lanka, Burma, Nepal, and Bhutan found primarily in upland forests and mountain slopes (4).

2.4. Cultivation

Ehretia laevis is a tropical plant that prefers direct sunlight to well-drained soil and partial shade. Cultivation requires a warm and humid environment with a temperature of 20 to 30 degrees Celsius. Seeds, cuttings and layering are all used for plant propagation. Sow seeds in nursery beds or polybags with 60-80% humidity (6). After 6-8 months, plant the seedlings in the field at a distance of 3-4 meters. During the growing season, use organic manure or fertilizer containing nitrogen, phosphorus and potassium (10:10:10). Regular watering, pruning and pest control ensures healthy growth. *Ehretia laevis* can grow up to 10 meters tall and has a lifespan of 20-30 years. Harvest the leaves, stems and roots as needed for medicinal use (7).

3. Methods used for extraction

Various methods of extraction used for extraction of phytoconstituents from *Ehretia laevis* are (4).

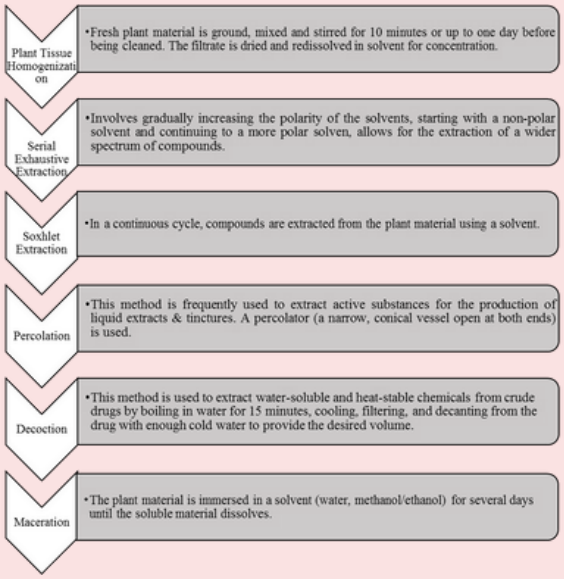


Figure 2. Extraction methods of phytoconstituents from *Ehretia laevis*

4. Phytochemical screening

Investigations have shown that the leaves, stem bark, root, fruit, seed of *Ehretia laevis* contain phytoconstituents, including primary metabolites and secondary metabolites from aqueous, ethanolic and ethyl acetate extracts (4).

Table 3. Phytochemical screening of *Ehretia laevis*

S.No.	Phytoconstituent	Part of Plant	Ethanolic extract	Aqueous extract	Ethyl acetate extract
1	Alkaloid	All Parts	+	-	-
2	Carbohydrates	All Parts	+	++	-
3	Triterpenoids	Leaves,Root, Seed	-	-	+
4	Phenolic Compounds	All Parts	+	+	-
5	Reducing sugar	Leaves,Stem bark, Root, Fruit	-	+	-
6	Flavonoids	Leaves,Stem bark, Fruit	+	+	+
7	Glycosides	Leaves,Root, Fruit, Seed	++	-	+
8	Sterols	All Parts	+	-	+
9	Saponins	Stem bark, Root	+	++	-
10	Proteins	Absent	-	-	-

5. Chemical constituents

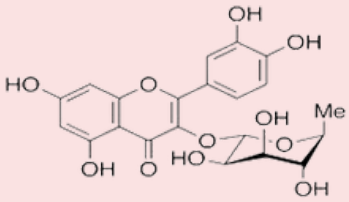
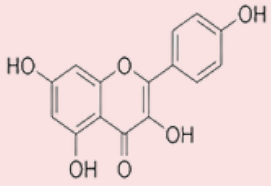
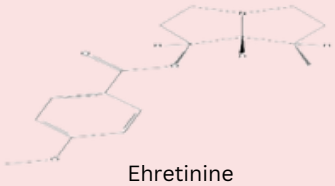
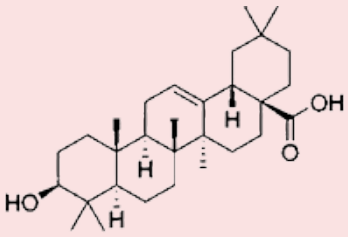
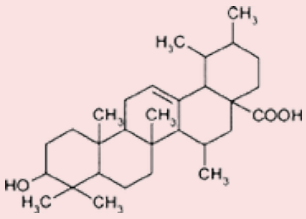
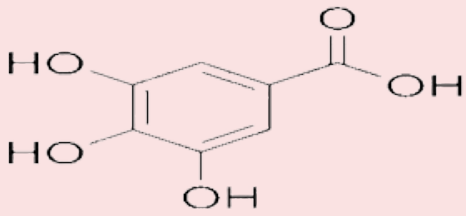
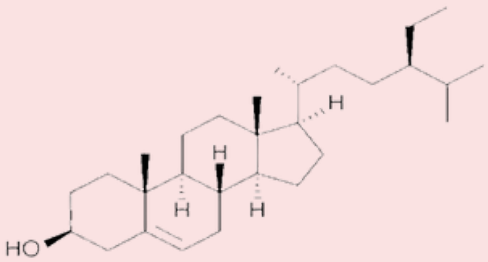
Table 4. Chemical constituents in parts of *Ehretia laevis* (8)

S. No.	Part	Chemical Constituent
1	Leaves	Rutin, Tannic acid, Ascorbic acid, naphthoquinone derivative minerals such as Sodium (Na), Calcium (Ca), Magnesium (Mg), Zinc(Zn), Copper (Cu), Lupeol, Gallic acid
2	Fruit	Betulin, Decanoic acid, phytol, piperazine,amyrin, phthalic acid, phenylephrine
3	Bark	Tannins, Baurinol, Phytol, Phenylephrine

Table 5. Chemical constituents & their role of *Ehretia laevis* (4)

S. No.	Chemical constituents	Role of chemical constituent
1	Flavonoid (Quercetin, kaempferol)	Antimicrobial, antioxidant, anti-inflammatory, anticancer and antimalarial
2	Decanoic acid	Antiseizure
3	Gallic acid	Treating Alzheimer's and Parkinson's disease by inhibiting the development of amyloid fibrils.
4	Phenylephrine	Decongestant,Hemorrhoids, vasopressor
5	β-sitosterol	Boost immunity and prevent influenza, rheumatoid arthritis, psoriasis
6	Decanoic acid	Antiseizure
7	Phytol	Antimalarial, Anti-inflammatory
8	α and β amyrin	Prevent persistent periodontitis-related bone loss.
9	Piperzine	Anti-helmintic
10	Phenylephrine	Decongestant, hemorrhoids, vasopressor
11	Betulin	Anti-inflammatory, Antipruritic, promotes skin cell differentiation, wound healing & cosmetic purposes. Inhibits the development of sterol regulatory element-binding protein (SREBPS) and reduces the production of cholesterol and fatty acids.
12	Lupeol	Chemoprotective, Anti-inflammatory and Antiprotozoal
13	Phthalic acid	Anti-viral against dengue, chikungunya
14	Ehretinine	Antimicrobial, anti-inflammatory, anticancer and antimalarial
15	Oleanolic acid	Antimicrobial, Neuroprotective, anti-inflammatory, anticancer and antimalarial

Table 6. Chemical structure of phytoconstituent (8)

S. No.	Phytoconstituent	Structure	
1	Flavonoids	 Quercetin	 Kaempferol
2	Alkaloids	 Ehretinine	
3	Saponins	 Oleanolic acid	 Ursolic acid
4	Phenolic acids	 Gallic acid	
5	Terpenoids	 β-Sitosterol	

6. Uses

Ehretia laevis, including its leaves, bark, stems, seeds and fruits, has long been used alone or in combination with other medicinal plants to treat various ailments.

Table 7. Uses of *Ehretia laevis* (10)

S.No.	Part of Plant	Preparation Used	Ailment/Use
1	All parts of plants	Decoction and juice	Abdominal pain
2	Root	Root extract	Acute and chronic inflammations
3	Fruits	Juice of fruits, decoction	Astringent, Diuretic, demulcent
4	Fruits and seeds	Decoction	Anthelmintic
5	Seeds	Three times a day, a paste made from soaked seeds and Amomum subulatum powder was administered with milk	Liver diseases/ jaundice
6	Bark	Bark paste has been used to treat pain, particularly in the lower limbs	Analgesic
7	Bark & stems	Decoction of stem and bark	Diphtheria
8	Powder of flowers	Flower powder mixed with the milk has been used as an aphrodisiac	Aphrodisiac
9	Powdered kernel	To treat ringworm infections, oil was combined with powdered kernel and administered topically to the afflicted region	Ringworm infection
10	Bark & leaves	Bark juice, leaf juice and decoction	Asthma, Malaria and fever
11	Leaves	Fresh leaves were used to make ghrit, which was then administered topically to the anal fissure twice daily for 21 days.	Fissure
12	Leaves	After making Kalka (paste), it was smeared all over the fracture.Cotton roll & pad were firmly applied.Kalka has a thickness of 0.5-1cm. For two weeks, this kalka Lepana was maintained in dressing for 24 hours per day.	Fracture
13	Leaves	Ten equal portions of leaf powder and sugar were combined & taken orally every day with goat milk or curd	Dysuria
14	Leaves	The leaves were mashed and wounds are treated topically with the resulting paste	Cuts and wounds
15	Leaves	The leaves were ground into powder and mixed with equal parts of sugar	Mouth blisters

7. Biological activity of *Ehretia laevis*

7.1. Anti-inflammatory activity

Ehretia laevis Roxb. extracts anti-inflammatory and antibacterial qualities were tested using agar well diffusion and carrageenan-induced rat paw edema. The results of the investigation showed that the aqueous, methanolic and chloroform extracts had significant anti-inflammatory efficacy (paw volume decreases). Outstanding antibacterial action against both Gram-positive like *Bacillus subtilis*, *Staphylococcus aureus* and Gram-negative like *Pseudomonas aeruginosa, Escherichia coli* bacteria, with the best efficacy being demonstrated by the methanolic extract activity against *Aspergillus niger* that is antifungal. According to these results, extracts from *Ehretia laevis* Roxb. Can be used as natural treatment for bacterial infections & inflammation (4).

7.2. Wound healing

Ehretia laevis is used for wound healing in Maharashtra, India's Wardha region, with promising outcomes. A paste prepared from *Ehretia laevis* leaves, which has a wide spectrum of antibacterial activity and may help cure anal fissures, was examined by Thakre et al. for its wound healing qualities (11).

7.3. Antimicrobial activity

Ehretia laevis Roxb, leaf extracts loaded silver nanoparticles shows: antimicrobial activity against various microorganisms, larvicidal activity (70% kill rate against Culex quinquefasciatus larvae), cytotoxic activity against HeLa (Henrietta Lacks) and MCF-7 (Michigan Cancer Foundation-7) cancer cells (LC50 (Lethal concentration): 12.7 and 14.5 µg/mL), dye degradation efficiency (~85% Congo red degradation within 8 hours). These nanoparticles have potential applications in water purification, cancer treatment, insect control and textile industry (6).

8. Marketed product

Khandu chakka oil is an ayurvedic medicine containing natural ingredients for effective pain relief, powerful blend of herbs and oils that works synergistically (8).

Figure 3. Khandu chakka oil

9. Conclusion

The synthetic medications are expensive, symptomatic, and often have a limited half-life. The inherent science of the *Ehretia laevis* was assessed, along with its scientifically proven properties, a safe and affordable method, and its medicinal uses which include anti-inflammatory, antimicrobial, antioxidant, and anticancer qualities that make them useful in the treatment of chronic illnesses. Additionally, it would be the greatest crop-cultivating opportunity to the farmers in terms of financial support.

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Phytopharmaceuticals: India's contribution to global health

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Abstract

India has enormous potential for the development of phytopharmaceuticals due to its vast biodiversity and extensive history of Ayurvedic medicine. This presents a promising approach for affordable and effective healthcare. Since prehistoric times, traditional remedies have made use of medicinal herbs. Plants are rich in bioactive compounds which are found in parts like the flowers, fruits, stems and leaves commonly referred to as phytochemicals. These elements support the requirements of the human body's systems. Phytopharmaceuticals have been employed extensively throughout the ages where both patients and medical professionals have recognized their greater therapeutic value and lower side-effect rates when compared with current medications. Targeting certain receptors, inhibiting disease pathways, and interrupting pathogenic life cycles are the main ways that phytopharmaceuticals work which hold promise in treating a spectrum of health conditions including oncological disorders, endocrine disorders, cardiovascular issues and neurodegenerative syndromes. Despite the potential benefits, challenges remain in integrating phytopharmaceuticals into mainstream medicine, such as addressing concerns over safety, drug interactions, and quality control. This review mainly focuses on significance, therapeutic applications, regulatory framework, challenges and future directions of phytopharmaceuticals.

Keywords: Phytopharmaceuticals, Medicinal herbs, Phytochemicals, Neurodegenerative syndrome, Endocrine disorders.

1. Introduction

Many natural products with diverse medicinal properties have been derived from plants and these resources are continuously investigated for the development of novel pharmaceuticals. These natural remedies have historically been employed by medical professionals to treat a wide range of illnesses. Several bioactive chemicals can be found in natural products. These bioactive substances provide immunity against several factors that cause disease (1). Plants have produced a wide variety of secondary metabolites with distinct structure and pharmacological characteristics. The knowledge preserved by the ancient medical system has made it possible to continue investigating medicinal plants with the intent to produce pharmaceuticals. The Department of Ayurveda, Unani, Siddha, and Homeopathy (AYUSH) and the Central Drugs Standards Control Organization (CDSCO) recently issued guidelines for the manufacturing of phytopharmaceutical medicines (PPDs), a novel type of herbal pharmaceuticals (2).

The words 'phyto' which means plant and 'pharmaceutical' which means medicinal products are the origin of the term "phytopharmaceutical." Since prehistoric times, traditional remedies involve the utilization of medicinal herbs. These plants have a range of bioactive substances or phytochemicals, within their fruits, flowers, stems, leaves and among the other components of the plant. These

constituents serve to augment the requirements of the human body's systems (3). The inherent features of the plant source are preserved while these substances are extracted analytically and then processed into dosage forms identical to those of traditional pharmaceuticals. Phytopharmaceuticals, in contrast to conventional herbal remedies, are tested through stringent procedures such as standardization, extraction, purification, and clinical validation in order to ensure reliability, efficacy, and consistency. Phytopharmaceuticals are classified into flavonoids, terpenoids, phytosterols, phytoestrogens, polyphenols, resveratrol, anthocyanins which is as shown in figure 1.

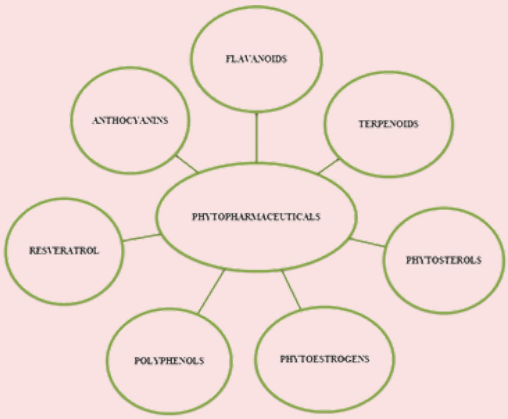

Figure 1. Classification of phytopharmaceuticals (1)

2. Significance of phytopharmaceuticals

Herbal remedies are widely regarded as a significant substitute for current allopathic treatment. Since ancient times, individuals have utilized herbal drugs for a variety of medical conditions. In developing nations, almost 80% of people use natural remedies to alleviate a range of disorders. India is referred to as the world's botanical garden and is one of the leading suppliers of medicinal herbs (4). These medications, that incorporate the therapeutic properties of plants instead of synthetic compounds, offer safer and more comprehensive treatment choices for a variety of conditions. Phytopharmaceuticals are becoming increasingly important in combating chronic illnesses like cancer, diabetes, cardiovascular disorders and neurological disorders. In addition, phytopharmaceuticals serve as a vital connection between traditional practices and current research, particularly in nations like India which has an extensive tradition of employing herbal remedies like Ayurveda. Table 1 provided a list of several phytopharmaceuticals and their medicinal applications (1).

Table 1. List of phytopharmaceuticals (1)

Phytopharmaceutical	Scientific name	Part of plant	Therapeutic use
Artemisinin	*Artemisia annu*	Leaf and aerial portion	Malaria treatment
Atropine	*Atropa belladonna*	Root, leaf, fruit	Impaired memory retrieval
Berberine	*Berberis vulgaris*	Fruit, root and stem	Diarrhea treatment
Caffeine	*Coffeaarabica*	Leaves and seeds	CNS stimulant
Cocaine	*Erythroxylum coca*	Leaves	CNS stimulant
Digoxin	*Digitalis lanata*	Leaves	Cardiotonic
Diosgenin	*Dioscorea deltoidea*	Leaf, stem, tuber	Antiproliferative
Ginsenosides	*Panax ginseng*	Root	Intellectual functioning
Morphine	*Papaver somniferum*	Latex	Analgesic
Quinine	*Cinchona ledgeriana, Cinchona peruvianbark*	Bark	Antimalarial

3. Therapeutic applications

3.1. Cancer

Cancer remains a major cause of mortality worldwide and is an extremely serious medical condition. The primary drawbacks of chemotherapy are drug resistance, cancer recurrence, and undesirable impact on non-specific cells that might reduce the feasibility of using chemotherapy treatments and worsen the quality of life for patients. Plant-based phytochemicals and derivatives offer intriguing alternatives to boost cancer patients' therapeutic effectiveness and reducing undesirable side effects. Vinca alkaloids, including vincristine and vinorelbine, along with podophyllotoxin analogs, are among the typical examples. These phytochemicals generally work by impacting molecular pathways that are associated with the progression and advancement of carcinoma. Increasing antioxidant status, eliminating carcinogens, preventing proliferation, causing cell cycle arrest and apoptosis, and immune system control are some of the specific methods (5).

3.2. Cardiovascular diseases

Terminalia arjuna, Commiphora mukul, Zingiber officinale, Withania somnifera, Daucus carota, Amaranthus viridis, and *Andrographis paniculate* are among the medicinal plants that are widely known for treating cardiovascular disease. Plant sterols, terpenoids, polyphenols, sulphur substances, and flavonoids are the bioactive plant derived chemicals present in these plants. Higher vasodilatation is facilitated by lower density lipoprotein oxidation is the way that flavonoids generally work. By lowering blood cholesterol absorption, plant sterols may mitigate cardiovascular disease (6).

3.3. Neurological disorders

Phytochemicalsmodulate the response of receptors for the significant inhibitory neurotransmitters which are vital for retaining the chemical balance of the brain. Multiple evidence suggests that plants are beneficial for treating neurological disorders in traditional medicine. *Curcuma longa, Terminalia chebula, Glycyrrhiza glabra, Hypericum perforatum, Ocimum sanctum* etc. are among the therapeutic plants that have demonstrated optimistic role in neuropsychopharmacological applications in the Indian medical system (7).

3.4. Infectious diseases

Phytopharmaceuticals, derived from plant-based compounds, are increasingly recognized for their efficacy in combating infectious diseases. They offer antimicrobial, antiviral, and immunomodulatory benefits, often with fewer side effects compared to synthetic drugs.While conventional medicines offer effective antibiotic treatments for bacterial infections, they are often associated with the issue of drug resistance. Consequently, numerous plants are widely utilized around the world as remedies for bacterial infections (8). Curcumin effectively suppresses the growth of both Gram-positive and Gram-negative bacteria.

3.5. Inflammatory disorders

Phytochemicals have the ability to inhibit the expression of genes that promote inflammation and enhance the expression of genes that prevent it; this variation in gene expression is modulated by epigenetic alterations (9). They have the potential to regulate inflammatory signalling pathways, including Nrf-2, MAPKs, NF-κB, and STAT signalling. Phytochemicals that exhibit anti-inflammatory effects include quercetin, bicyclol, capsaicin, escin, and colchicine.

The phytopharmaceuticals currently undergoing clinical trials are as follows:

A purified aqueous extract of *Cocculus hirsutus* (AQCH) is a phytopharmaceutical drug being investigated as a potential novel therapy for COVID-19.AQCH exhibited significant antiviral properties in laboratory-based studies and in a dengue animal model (10). The development of two phytopharmaceutical candidates, *Cannabis sativa* for pain relief and *Boswellia serrata* for treating rheumatoid arthritis, is being carried out through a collaborative agreement among the Council of Scientific & Industrial Research (CSIR), the Department of Biotechnology (DBT), and the Indian Council of Medical Research (ICMR). This partnership emphasizes inter-ministerial cooperation aimed at advancing innovative research in the field of phytopharmaceuticals (11).

4. Regulatory framework

In India, phytopharmaceuticals are governed under the Drug and Cosmetic Act (D and C) 1940 and Rules 1945, which have specific rules for Siddha, Ayurvedic, and Unani medicine. The definition of a "phytopharmaceutical drug" is stated as a purified and standardized fraction of an extract of a medicinal plant or a portion of it that contains a minimum of four bio-active or phytochemical substances intended for internal or external use by humans or animals for the prevention, treatment, mitigation, or diagnosis of any disease or disorder but exclude parenteral administration. The recent addition of Schedule Y's Appendix I B outlines the information that must be included with the application in so as to import, manufacture, or accomplish clinical research for a phytopharmaceutical medicine in the country. The NDA for the phytopharmaceutical drug must comply with regulatory standards for research on humans, validating clinical research, and innovative drug safety and pharmacological information (12).

The Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy (AYUSH), which monitors regulations, mandates that all manufacturing and marketing of herbal medications be done after acquiring the required manufacturing approvals (13). The Government of India's Ministry of Health and Family Welfare published a notice outlining the phytopharmaceuticals legal requirements. Valid scientific evidence addressing the quality, safety, and efficacy of pharmaceuticals in contrast to synthetic chemical substances is one of these prerequisites. Central Drugs Standards Control Organization (CDSCO) holds accountability for phytopharmaceuticals (4). The processes and difficulties of the phytopharmaceutical development process are depicted in Figure 2

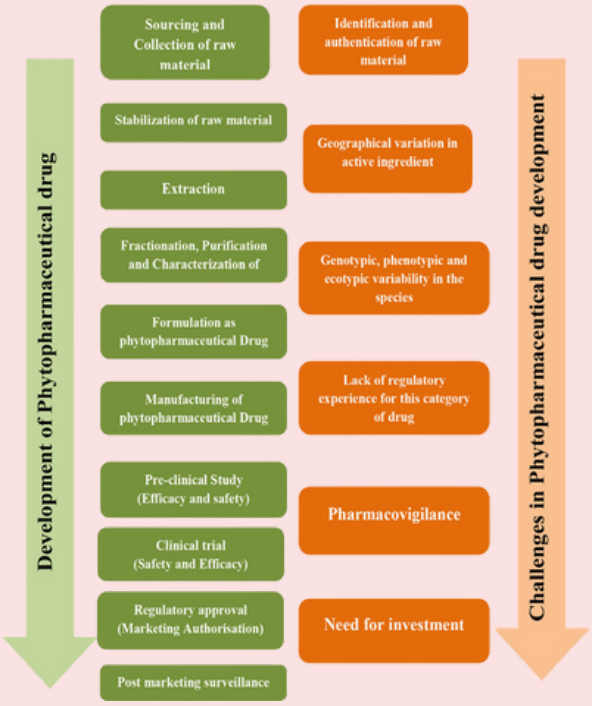

Figure 2. Development process and challenges of phytopharmaceuticals (14)

5. Future prospects

The demand for phytopharmaceuticals has expanded as a result of people's expanding acceptance of them due to their benefits, and the volume of these products entering the global market is constantly expanding. Recent advances in the administration and application of plant-based phytomedicines, nanophytomedicine is opening up novel possibilities for the phytopharmaceutical sector and offering a plethora of new antimicrobials. Nanophytomedicine minimizes toxicity and potential side effects for the patient while simultaneously enhancing the drug's bioavailability and efficacy (15). Nanocarriers loaded with berberine are utilized to enhance its bioavailability and therapeutic potential. Berberine, a natural alkaloid, possesses notable anti-inflammatory, antioxidant, and anti-fibrotic effects, making it effective in various medical applications (16). Quercetin-loaded nanoemulsions are developed for their antioxidant and anticancer activities, providing better absorption and targeted delivery. The research and development of phytopharmaceuticals is anticipated to concentrate on tackling significant global health issues like cancer, antimicrobial resistance, and chronic diseases. This is made feasible by advancements in biotechnology, nanotechnology, and regulatory support.

6. Conclusion

Plant derived drugs have played a crucial role in human health since time immemorial. Medicines made from plants and their parts have been used for a variety of illnesses since ages past.Plants continue to serve an important role in healthcare worldwide, even with the tremendous advances in modern medicine over the last few decades. Phytopharmaceuticals offer a promising alternative to synthetic medicines, offering remedies with fewer adverse effects and greater patient acceptability, especially for chronic and lifestyle-related diseases such as diabetes, hypertension, and neurodegenerative disorders. India has the potential to establish a strong ecosystem that not only meets the country's healthcare requirements but also taps into the expanding worldwide market for herbal medicines by placing a strong emphasis on rigorous research, quality assurance, and regulatory compliance. The phytopharmaceutical sector holds the potential to propel revolutionary progress in the healthcare and economic fields. The country can satisfy the growing demand for natural medicines worldwide while promoting innovation and economic growth within the nation by emphasizing on standardization, clinical validation, and sustainable sourcing. India will play a significant and ground-breaking role in the phytopharmaceutical revolution as the entire world looks more and more toward natural, sustainable healthcare solutions.

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Phytopharmaceuticals in India 2024: A fusion of tradition and modern science

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Abstract

The phytopharmaceutical sector in India is witnessing a surge in growth in 2024, driven by regulatory support, technological advancements, and a convergence of traditional knowledge with modern science. Phytopharmaceuticals, defined as standardized plant-based drugs with multiple bioactive compounds, are subject to rigorous scientific evaluation, aligning India's regulatory framework with international standards like the FDA's botanical drug guidelines. Recent innovations, particularly in nanotechnology, have improved the bioavailability and therapeutic efficacy of phytopharmaceuticals, with promising applications in cancer treatment. The Indian government's supportive regulations, introduced in 2015, have fostered innovation, leading to increased research and investment in this field. Indian researchers are also leveraging indigenous knowledge from traditional systems like Ayurveda to validate and develop new therapies, including promising developments with turmeric-based phytopharmaceuticals such as Curcumin. These advancements highlight India's growing influence in the global phytopharmaceutical market, as it integrates traditional medicine with cutting-edge research to develop novel plant-based drugs.

Keywords: Phytopharmaceuticals, Nanotechnology, Curcumin, Bioavailability, Ayurveda

1.Introduction

Phytopharmaceuticals, plant-based drugs that meet the rigorous standards of modern medicine, have seen tremendous growth in India in recent years. As 2024 unfolds, the country's advancements in this sector are gaining global attention (1). These developments are reshaping the way botanical-based drugs are researched, developed, and utilized, aligning India with global trends in natural therapeutics.

2. Regulatory advancements: Paving the way for innovation

The Indian government, through the CDSCO, introduced a pivotal regulatory framework in 2015 that sets rigorous scientific standards for the approval of phytopharmaceuticals. This shift aligns India's standards with those of international agencies like the FDA, establishing strict criteria for clinical trials, safety evaluations, and quality control (1). This framework has been instrumental in attracting investments and accelerating research in phytopharmaceuticals, driving innovations such as high-bioavailability formulations and standardized extracts. Specifically, Curcumin's regulatory journey demonstrates the potential of such frameworks: its approval processes have leveraged both traditional knowledge and modern clinical research, creating a reliable therapeutic profile within the Indian phytopharmaceutical landscape.

The Indian government's proactive role in regulating phytopharmaceuticals is at the heart of this boom. Introduced in 2015, the Central Drugs Standard Control Organization (CDSCO) issued a framework that treats phytopharmaceuticals similarly to synthetic drugs, mandating comprehensive scientific evaluation of safety, efficacy, and quality before approval. This regulatory clarity has attracted significant investment from pharmaceutical companies and research institutions alike (2).

As shown in Table 1, regulatory differences between traditional herbal medicines and phytopharmaceuticals demonstrate the rigorous scientific standards required for modern phytopharmaceuticals compared to traditional herbal therapies, which are based on historical use and traditional knowledge.

Table 1. Regulatory differences between traditional herbal medicines and phytopharmaceuticals (3)

Parameter	Traditional Herbal Medicines	Phytopharmaceuticals
Approval Requirements	Historical use, traditional knowledge	Scientific data on quality, safety, efficacy
Regulatory Body	AYUSH	CDSCO
Testing	Minimal	Rigorous clinical trials
Classification	Ayurvedic, Unani, Siddha	New Chemical Entity (NCE)

3. Technological breakthroughs: Merging tradition with modern science

In addition to nanotechnology, other significant technological innovations are driving the progress of phytopharmaceuticals. For instance, High-Throughput Screening (HTS) enables rapid testing of thousands of plant extracts or compounds, which speeds up the discovery of bioactive molecules with potential therapeutic uses. Bioinformatics and computational tools have transformed our understanding of plant compounds, allowing for in silico predictions of molecular interactions and safety profiles, which reduces the reliance on early-stage animal testing (4).

Advanced extraction techniques are also central to this progress. Supercritical Fluid Extraction (SFE) and Microwave-Assisted Extraction (MAE) provide efficient, non-toxic methods for extracting bioactive compounds, preserving their potency and purity. These methods help improve the consistency, safety, and efficacy of plant-based drugs, making them more suitable for standardized phytopharmaceutical formulations.

In addition to nanotechnology, significant advancements such as high-throughput screening (HTS), bioinformatics, and advanced extraction techniques (e.g. supercritical fluid extraction, microwave-assisted extraction) are reshaping the landscape of phytopharmaceuticals. HTS allows rapid screening of bioactive compounds, bioinformatics facilitates in silico testing to reduce early-stage animal testing, and improved extraction methods ensure purity and efficacy. Further innovations in metabolomics, chemometrics, and genetic engineering (e.g., CRISPR/Cas9) enable more precise formulation and sustainable production of plant-derived pharmaceuticals, supporting consistent quality and targeted therapeutic outcomes.

One of the most exciting developments in this space is the adoption of nanotechnology to enhance the efficacy of plant-based drugs (3). Nanophytomedicine, which uses nano-formulations of phytochemicals, improves drug absorption, stability, and bioavailability. This technology has been particularly promising in cancer research, where plant-based compounds are gaining attention for their anti-cancer properties.

3.1. **High-throughput screening (HTS):** High-throughput screening has revolutionized the discovery of bioactive compounds from plants. It allows rapid and simultaneous testing of thousands of plant extracts or isolated compounds for potential therapeutic activity. In phytopharmaceutical research, HTS identifies plant-derived molecules with specific pharmacological properties, such as anti-inflammatory, anticancer, or antimicrobial effects (5). This speeds up the drug discovery process by providing faster access to promising bioactive compounds, enabling more efficient identification of candidates for further study.

3.2. **Bioinformatics and computational approaches:** The integration of bioinformatics and computational biology into phytopharmaceutical research has expanded our understanding of plant-based medicines. Bioinformatics tools help in the prediction of molecular interactions between plant-derived compounds and their biological targets, facilitating drug design and development. These tools also enable researchers to predict the safety profiles of phytochemicals by assessing their pharmacokinetics and toxicity profiles in silico, reducing the need for early-stage in vivo testing. Computational databases containing ethnobotanical and phytochemical information are helping streamline the discovery of new therapeutic agents from medicinal plants.

3.3. **Advanced extraction techniques:** Innovations in extraction techniques are improving the yield, purity, and consistency of bioactive compounds from plants. Some advanced methods include:

- Supercritical fluid extraction (SFE): This technique uses supercritical CO_2 to extract bioactive compounds without using toxic solvents, preserving the purity and integrity of the compounds. SFE is especially useful for heat-sensitive phytochemicals, ensuring their bioavailability and potency (4).
- Microwave-assisted extraction (MAE): MAE is a rapid and efficient method of extracting plant compounds using microwave energy. It accelerates the extraction process while preserving the bioactivity of compounds, making it highly suitable for large-scale production of phytopharmaceuticals.
- Ultrasound-assisted extraction (UAE): UAE enhances extraction efficiency by using ultrasonic waves to disrupt plant cell walls, leading to better release of active ingredients. This method is particularly useful in extracting compounds from hard-to-process plant materials, improving the yield of pharmacologically active ingredients.

3.4. **Metabolomics and chemometric techniques:** Metabolomics is the large-scale study of small molecules, or metabolites, in plants. This technology enables researchers to map the complex chemical profiles of medicinal plants and identify which metabolites contribute to therapeutic effects. Metabolomic profiling can differentiate between closely related plant species, ensuring that only the correct and most potent species are used for drug development. Chemometrics, which involves the statistical analysis of chemical data, complements metabolomics by allowing researchers to optimize extraction methods and ensure the consistency of phytopharmaceutical products (6).

3.5. **Precision formulation techniques(9):** Recent advances in formulation technologies, such as liposomes, solid lipid nanoparticles (SLNs), and polymeric nanoparticles, have been employed to improve the bioavailability of plant-based drugs. While nanotechnology has been a key player, beyond that, innovative encapsulation techniques protect phytochemicals from degradation and enhance their absorption in the body, addressing the issue of poor solubility often faced with plant-derived compounds. Such advancements ensure that the therapeutic compounds in phytopharmaceuticals are delivered more efficiently to target tissues, leading to more reliable therapeutic outcomes.

3.6. **Pharmacovigilance and post-marketing surveillance:** Digital technologies like electronic health records (EHRs) and mobile health applications are being leveraged for better pharmacovigilance in the field of phytopharmaceuticals. These innovations help monitor the safety and efficacy of plant-based medicines post-marketing, providing real-time data on adverse events, drug interactions, and patient outcomes. This feedback loop enables continuous improvement in the safety profiles of phytopharmaceuticals(6).

3.7. **Genetic engineering and plant cell cultures:** Biotechnological advancements, including genetic engineering, are being applied to optimize the production of specific bioactive compounds in plants. Techniques such as CRISPR/Cas9 gene editing allow for the enhancement of metabolic pathways within plants, leading to increased production of desired phytochemicals. Similarly, plant cell cultures enable the sustainable production of bioactive compounds without the need for extensive cultivation, reducing environmental impact and ensuring a stable supply of raw materials for phytopharmaceutical development(7).

extensive cultivation, reducing environmental impact and ensuring a stable supply of raw materials for phytopharmaceutical development(7).

As seen in Table 2 nanophytomedicine offers significant improvements over traditional phytotherapy, particularly in terms of absorption, stability, and targeted delivery, which makes it promising for use in managing chronic diseases effectively reference from Nayak D et.al

Table 2. Comparison of traditional phytotherapy vs. nanophytomedicine (6)

Aspect	Traditional Phytotherapy	Nano phytomedicine
Absorption	Low	High
Stability	Limited	Enhanced
Targeted Delivery	No	Precise
Use in Chronic Diseases	Limited	Promising

4. Research focus: Exploring India's traditional knowledge

India's vast repository of traditional medicinal knowledge has also played a role in fuelling innovation. Researchers are increasingly working with traditional practitioners to scientifically validate the medicinal properties of plants used in Ayurveda and other traditional systems (4). Phytopharmaceuticals based on plants like Ashwagandha, Turmeric, and Neem are now being tested for their efficacy in treating chronic diseases such as diabetes, inflammation, and neurodegenerative disorders.

5. Case study: Turmeric-based phytopharmaceuticals

Curcumin, derived from turmeric, has emerged as a potent agent with anti-inflammatory, antioxidant, and anticancer properties. Despite its promising therapeutic potential, curcumin has traditionally suffered from low bioavailability. Recent nano-formulations, such as liposomal curcumin and polymeric nanoparticles, have enhanced its bioavailability, making it more effective in the treatment of chronic conditions like cancer and arthritis.

In addition to nanotechnology, curcumin has also benefited from bio-enhanced extraction methods. Using supercritical fluid extraction, researchers have succeeded in isolating purer, more stable curcumin extracts, while bioinformatics tools have predicted its interaction with various cellular pathways, providing a basis for targeted therapeutic applications (7). These advancements underline curcumin's value in modern phytopharmaceuticals, transforming it from a traditional remedy into a scientifically validated treatment option.

Curcumin, derived from turmeric, has proven anti-inflammatory, antioxidant, and anticancer benefits. However, its traditionally low bioavailability has limited its therapeutic potential. Recent advancements, including liposomal and polymeric nanoparticles, have significantly improved its absorption and stability, making it effective for conditions like cancer and arthritis. Ongoing clinical research is examining curcumin's efficacy in more complex chronic conditions, highlighting challenges in large-scale production but reinforcing its position as a potent therapeutic agent.

One of the most successful examples is the development of Curcumin-based phytopharmaceuticals from turmeric. Curcumin, the active compound in turmeric, has shown promise in treating inflammation and cancer (5). Indian companies are now developing highly bioavailable forms of curcumin using nano-formulations, making it more effective for therapeutic use (6).

6. Conclusion

India's phytopharmaceutical industry is poised for substantial growth, driven by technological

advancements, regulatory support, and a blending of traditional knowledge with modern scientific methodologies. However, the sector also faces challenges that may impact its long-term viability. Issues such as sustainability in sourcing raw materials, competition from both domestic and global markets, and the need for continued regulatory adaptation to keep pace with evolving research are critical considerations for future growth. Addressing these challenges will be essential to sustain the momentum of India's phytopharmaceutical sector and secure its role in the global market for plant-based therapies.While the Indian phytopharmaceutical industry is positioned for substantial growth, certain challenges need to be addressed for sustained momentum. Sustainability issues in sourcing raw materials, growing market competition, and the necessity for ongoing regulatory adaptation to align with global standards pose potential barriers. Addressing these challenges will be critical to secure India's role as a leader in the global phytopharmaceutical market and to maintain ethical, environmentally-conscious production practices.

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Phytopharmaceuticals: India's growing market potential

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Abstract
India's phytopharmaceutical industry is uniquely positioned in the global market due to its vast biodiversity, encompassing over 7,500 medicinal plant species, and a deep-rooted foundation in traditional medicinal systems such as Ayurveda, Siddha, and Unani. Recent regulatory advancements, including the 2015 amendment to the Drugs and Cosmetics Act, and innovations in biotechnology and nanotechnology have elevated the quality, safety, and efficacy of Indian phytopharmaceuticals. The sector's growth contributes significantly to economic development and healthcare access, particularly for chronic disease management. Addressing quality standardization and intellectual property protection will further strengthen India's potential as a global leader in plant-based therapeutics.

Keywords: Phytopharmaceuticals, Ayurveda, Traditional Medicine, Biodiversity, Biotechnology, Nanotechnology, Intellectual Property

1. Introduction
India's phytopharmaceutical industry possesses a combination of unique strengths that position it well in the global market. With over 7,500 medicinal plant species spread across diverse ecosystems, India provides a vast reservoir of bioactive compounds essential for the development of plant-based therapeutics. This rich biodiversity supports India's potential to treat complex, multifactorial diseases, including cancer, diabetes, and neurodegenerative disorders. The country's extensive traditional medicinal systems—Ayurveda, Siddha, and Unani—form an unparalleled knowledge base with over 3,000 years of historical use. These systems are holistic, multi-component therapies that align with modern phytopharmaceutical approaches, emphasizing the synergistic effects of complex mixtures of bioactive compounds (1).

Regulatory advancements further underscore India's capabilities. The 2015 amendment to the Drugs and Cosmetics Act introduced specific regulatory pathways for phytopharmaceuticals, establishing quality, safety, and efficacy standards aligned with international benchmarks. This regulatory support allows Indian phytopharmaceuticals to undergo rigorous clinical trials and adhere to Good Manufacturing Practices (GMP), ensuring both credibility and safety in global markets. Initiatives like the National Medicinal Plants Board (NMPB) encourage sustainable and ethical sourcing, conserving biodiversity and creating benefit-sharing agreements with indigenous communities. These sourcing practices adhere to environmental and social governance standards, adding further value to India's phytopharmaceutical products (2).

India's technological advancements in fields such as biotechnology and nanotechnology enhance its strengths in phytopharmaceutical production. Advanced techniques like plant tissue culture for

sustainable production and nanocarrier systems for enhanced drug delivery improve bioavailability and therapeutic efficacy, ensuring that India's phytopharmaceuticals are competitive with synthetic medicines on a global scale (3).

2. Economic and healthcare impact

The economic and healthcare impacts of India's phytopharmaceutical growth are substantial. Globally, the phytopharmaceutical industry is projected to reach over USD 100 billion by 2025, with India and other Asia-Pacific nations driving a significant portion of this growth. Phytopharmaceuticals contribute to India's economy by creating employment opportunities, particularly in rural and biodiversity-rich regions where medicinal plant cultivation is promoted by the government. Jobs across the supply chain—spanning raw material sourcing, R&D, manufacturing, and quality control—provide economic stability and reduce rural-to-urban migration (4).

India's phytopharmaceutical exports add value to its GDP, with growing demand in North America, Europe, and Southeast Asia. Government policies such as subsidies for medicinal plant cultivation and export incentives bolster this growth, positioning India as a key player in global phytopharmaceutical supply chains (5).

In healthcare, phytopharmaceuticals offer cost-effective options for managing chronic diseases that burden healthcare systems, including diabetes, hypertension, arthritis, and certain cancers. Plant-based products, such as curcumin from *Curcuma longa,* provide a cost-effective and accessible alternative to synthetic drugs, particularly in rural areas where traditional medicine is culturally accepted and often more affordable than conventional treatments. Phytopharmaceuticals are also integrated within formal healthcare systems, promoting an evidence-based approach to traditional remedies and reducing adverse drug reactions associated with synthetic medications. The use of phytopharmaceuticals in preventive and primary care further enhances accessibility, providing comprehensive healthcare solutions that cater to diverse socioeconomic groups (6).

3. India's potential as global leader

India's abundant resources, government support, and scientific expertise collectively strengthen its potential to lead the global phytopharmaceutical sector. The Ministry of AYUSH, the NMPB, and the Traditional Knowledge Digital Library (TKDL) play essential roles in preserving traditional knowledge and fostering innovation. The regulatory framework introduced by the 2015 amendment to the Drugs and Cosmetics Act provides a clear pathway for phytopharmaceuticals, setting globally competitive standards that reinforce India's reputation as a trusted supplier (7).

India's scientific expertise in pharmacognosy, biotechnology, and nanotechnology further contributes to its leadership potential. R&D efforts in bioavailability, targeted delivery, and clinical efficacy address key challenges in phytopharmaceuticals, ensuring India's products meet international standards. Collaboration with global research institutions will support an innovation pipeline of next-generation phytopharmaceuticals, enabling India to meet the growing global demand for effective, natural healthcare products (8).

4. Global integration and standardization

Global integration and standardization of India's phytopharmaceuticals are achievable through harmonized quality standards, research investments, and international regulatory participation. Building on the 2015 regulatory amendment, India can align its quality and safety standards with those of agencies like the FDA and EMA, facilitating cross-border approvals and trade. Investing in R&D on bioavailability, controlled release formulations, and clinical efficacy will help India's phytopharmaceuticals maintain consistent performance across global markets. Partnerships with international institutions can further foster innovative solutions tailored to diverse healthcare needs (9).

Intellectual property (IP) protection remains critical for phytopharmaceutical growth. India's TKDL effectively catalogs traditional formulations, preventing unauthorized patents and biopiracy. However, frameworks that offer IP protection for scientifically validated adaptations of traditional knowledge are needed. Adapting a "sui generis" approach, which balances IP rights with communal ownership, could address this need, protecting India's innovations while honoring traditional sources (10).

Participation in global regulatory forums such as WHO and ICH can help India contribute to standardizing phytopharmaceutical quality, safety, and efficacy worldwide. As global interest in plant-based medicines rises, India's regulatory and scientific expertise would allow it to shape global standards for phytopharmaceuticals, supporting widespread acceptance and integration of Indian products (11).

5.Successful products and initiatives

5.1. Himalaya's Liv.52

This hepatoprotective formulation combines *Capparis spinosa* and *Cichorium intybus* extracts, supporting liver function and treating hepatitis and cirrhosis. Available in over 60 countries, Liv.52 has become a flagship example of a successful, clinically validated Indian phytopharmaceutical product.

5.2. Dabur's Chyawanprash

With over 40 herbs, including *Phyllanthus emblica* and *Withania somnifera*, Chyawanprash is widely used in India for immunity enhancement and general wellness. Dabur's adherence to quality standards and clinical validation has made Chyawanprash popular in both domestic and international markets.

5.3. Patanjali's Divya Mukta Vati

Targeted at hypertension, Divya Mukta Vati combines *Terminalia arjuna* and *Bacopa monnieri*, offering a plant-based solution for blood pressure management. Patanjali's focus on affordability has made the product accessible to lower-income groups, expanding its reach in both rural and urban areas (12).

5.4. Zandu Kesari Jivan

Designed for geriatric care, Kesari Jivan includes *Asparagus racemosus, Mucuna pruriens,* and *Piper longum* to support cognitive and physical health in elderly populations. Zandu's quality standards have helped the product gain a stable presence in international markets focused on aging populations (12).

5.5. CSIR-IIIM Anti-Cancer Phytopharmaceutical

CSIR and the Indian Institute of Integrative Medicine collaborated to develop an anti-cancer drug derived from *Boswellia serrata*. This partnership highlights India's growing expertise in phytopharmaceutical oncology research (13).

5.6. Traditional Knowledge Digital Library (TKDL)

The TKDL protects India's traditional knowledge, cataloging thousands of formulations to prevent biopiracy. The TKDL model has been effective in thwarting unauthorized patents, supporting ethically responsible phytopharmaceutical development (14).

6. Training and workforce development

Building a skilled workforce is essential for India's global phytopharmaceutical leadership. Expertise in pharmacognosy, phytochemistry, and quality control is critical to meet international standards. Educational programs and hands-on training modules in advanced extraction techniques, standardization, and GMP compliance are necessary to equip professionals with the required skills. Industry-academia collaboration can further support workforce development through internships and certification programs. Institutions like CSIR and the Ministry of AYUSH can play pivotal roles by providing research opportunities that combine technical and regulatory training, preparing a workforce capable of tackling global phytopharmaceutical challenges (15).

7. Intellectual property and patent issues

Intellectual property protection presents unique challenges for phytopharmaceuticals, particularly regarding traditional knowledge. While the TKDL has been successful in preventing biopiracy, further frameworks are required to support IP protections for modernized or scientifically adapted formulations of traditional remedies. A sui generis IP system could offer limited exclusivity for

products that significantly advance traditional formulations, thereby balancing IP protection with communal knowledge preservation (16).

8.Global market competition

Table 1. Global Market Trends comparing strengths, weaknesses and advantages of India, China, Germany and The U.S. (WHO, 2022; Coherent Market Insights, 2023; Research and Markets, 2023; Global Data, 2022)

Country	Strengths	Weaknesses	Competitive Advantage
India	Biodiversity, traditional knowledge (Ayurveda, TKDL), government support (AYUSH, NMPB), cost-effective R&D	Quality variability, regulatory challenges, IP issues with traditional knowledge	Low-cost production, vast plant resources, strong R&D in traditional systems (17, 20).
China	Extensive TCM tradition, established global trade network	Limited standardization, concerns over resource sustainability	Global TCM export network, cultural integration of traditional medicine (18).
Germany	Rigorous quality standards, strong regulatory framework (Commission E)	High production costs, limited biodiversity	Trusted healthcare products, strong quality assurance (19).
U.S.	Advanced biotech R&D, FDA Botanical Drug Development Pathway	High regulatory barriers for herbal products, limited biodiversity	Advanced R&D infrastructure, consumer trust in regulated natural health products (20).

India's strengths like biodiversity, traditional knowledge, and cost-effective production position it well against established competitors. To increase its competitiveness, India must address quality variability and enhance its regulatory alignment with international markets. Compared to China’s stronghold in Traditional Chinese Medicine (TCM) and Germany and the U.S.'s rigorous quality standards, India’s advancements in cost-effective R&D and ethical sourcing give it a distinct edge, particularly in price-sensitive markets (21).

8. Conclusion

India’s phytopharmaceutical industry holds strong potential to become a global leader in plant-based therapeutics due to its rich biodiversity, extensive traditional knowledge systems, and supportive regulatory frameworks. With advancements in biotechnology and nanotechnology, India can enhance the efficacy and global competitiveness of its phytopharmaceuticals. Sustainable sourcing, adherence to Good Manufacturing Practices (GMP), and strategic international partnerships further solidify India's position in the industry. Addressing challenges like quality variability and intellectual property rights for traditional knowledge will be key for India to strengthen its global market presence and contribute significantly to accessible, holistic healthcare solutions worldwide.

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CONSAP

Answers are on page 227

A review of traditional and modern science convergence in Indian phytopharmaceuticals


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Abstract

Phytopharmaceuticals are a distinct category of plant-based medicines that combine the rich heritage of traditional knowledge with the rigor of modern science. With their standardized production, scientific validation, and adherence to quality and safety standards, phytopharmaceuticals bridge the gap between traditional herbal medicine and modern pharmaceuticals, offering effective, reliable, and safe treatment options. The search for bioactive molecules in medicinal plants can be guided by traditional knowledge, which could result in the discovery of novel phytochemicals. A strong basis for the development of phytopharmaceuticals is provided by unique position of India as a leader in both traditional medicine and modern pharmaceutical innovation. The fast expanding pharmaceutical industry in India that ranks among the world's largest in terms of both production and export, supplements the centuries-old traditional medical culture of India, including Ayurveda, Siddha, and Unani. Because of these two advantages, India is able to create a thriving ecosystem for the development of plant-based medicines by bridging the gap between traditional knowledge and modern science.

Keywords: Ayurveda, Modern science, Phytopharmaceuticals, Traditional knowledge

1. Introduction

Phytopharmaceuticals refer to the bioactive compounds that have been isolated from plant sources which exhibit pharmacological activity. Herbal medicines containing single or multiple phytoconstituents having biological activities are also considered as Phytopharmaceuticals. Indian culture is well versed with several medical treatments developed from plants or parts of plants based on ancient knowledge. India is also known as botanical garden of the world as it is one of the large scale producers of medicinal plants. Along with supporting the maintenance of all the physiological functions in the human body, phytopharmaceuticals exhibit pharmacological actions like specific targeting of biological receptors, blocking of disease related pathways, and the breaking of life cycles of pathogens. Even though the herbal remedies are very much popular in the society, only few medicinal plants have been identified through scientific evaluation for their pharmacological potential. But, these herbal drugs are not regulated properly and many times they are not registered or not even controlled by health authorities. There is an urgent need to discover more Phytopharmaceuticals, identify their sources, evaluate their pharmacological activities and prepare their standardised formulations.

2. Definition of phytopharmaceuticals

Central Drugs Standard Control Organization (CDSCO) has designed the Guidelines for Phytopharmaceuticals in India. According to these guidelines, phytopharmaceuticals are defined as "the purified and standardized fractions with a defined minimum percentage of a bioactive or phytochemical compound, prepared from medicinal plant materials using appropriate processes and marketed for a specific indication or therapeutic use". This gives exact idea of how the phytopharmaceuticals are different from conventional herbal medicines and synthetic drugs and it also sets standards for reproducibility, consistency, and quality of the phytopharmaceutical product (1). As per D and C act 1940, Phytopharmaceutical drugs include purified and standardized fraction with defined minimum four bioactive or phytochemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include administration by parenteral route (2).

3. Key characteristics of phytopharmaceuticals

3.1. Standardization and quality control

Phytopharmaceuticals are standardized in a manner to get a specific percentage of bioactive components (e.g., flavonoids, alkaloids, or terpenes), in contrast to traditional herbal remedies, which might vary in effectiveness due to factors including plant growth circumstances and extraction processes. Analytical testing, the application of proven extraction and purification methods, and the selection of premium raw materials are the steps in this process. For example, Liu et al. (2021) reported that standardized *Ginkgo biloba* extracts contain nine biginkgosides, a new type of flavonol glycosides, six new flavonol glycosides, a new sesquiterpene, and three new nor-sesquiterpenoids (3).

3.2.Purity and safety

To ensure that the finished phytopharmaceutical product is safe for consumption, the impurities and potentially hazardous substances (such as pesticides, heavy metals, and microbiological contamination) are eliminated during processing. Considering the variation in plant components, which can compromise safety if unchecked, this purification procedure is especially crucial. According to a study by Klein-Junior et al. (2021), the contaminants in raw plant materials can lead to adverse health effects and, if left unchecked, can reduce the therapeutic effectiveness of phytopharmaceuticals. This emphasizes the significance of purification and quality inspections (4).

3.3. Scientific validation and clinical trials

Phytopharmaceuticals, in contrast to many conventional herbal remedies, undergo thorough scientific testing, including *in vitro* (lab) and *in vivo* (animal and human) investigations. For example, *curcumin,* a phytoconstituent obtained from *Curcuma longa*, has been the subject of extensive research, and clinical trials have demonstrated its effectiveness in lowering inflammation and curing a number of illnesses. Due to their proven safety and effectiveness characteristics, products with standardized *curcumin* extracts are now often used as phytopharmaceuticals (5). The anti-malarial medication, artemisinin, which is made from *Artemisia annua* (sweet wormwood) is a well-known example of herbal medicine. Modern malaria treatment procedures now heavily rely on artemisinin-based medicines due to this understanding of its mechanism (6).

3.4. Regulatory compliance and good manufacturing practices (GMP)

Strict regulatory standards, such as good manufacturing practices (GMP), are followed during the production of phytopharmaceuticals to guarantee their consistency, superior quality, and consumer safety. To be marketed as pharmaceutical-grade, phytopharmaceuticals must adhere to strict production, labeling, and quality criteria set by regulatory bodies like the U.S. FDA and the CDSCO in India. The stability and quality of plant-based products can be affected by variables like temperature, humidity, and cleanliness. Regulatory compliance, which guarantees the safety and effectiveness of phytopharmaceuticals, has helped to increase their adoption in mainstream healthcare (7).

3.5. Bioavailability and novel formulations

Novel formulations including liposomes, nanoparticles, and encapsulation can greatly increase the bioavailability of certain plant-based substances, such as curcumin, which makes them more effective as medicines. The therapeutic potential of plant-based medications is increased by these

sophisticated formulations, which allow for targeted distribution and regulated release of active ingredients. For example, nano-curcumin is a more powerful antioxidant and anti-inflammatory due to its enhanced absorption and bioactivity (8).

4. Historical context of phytopharmaceuticals

With deep roots in the history of medicine, plants have been the primary source of healing. Based on the curative qualities of plants, traditional medical systems including Western herbalism, Ayurveda in India, Traditional Chinese Medicine (TCM), and Unani all evolved complex procedures and vast materia medica.

4.1. Ancient beginning

Use of plants for the treatment of various diseases has been initiated since ancient ages. The evidences for this have been found in various texts, records, pharmacopoeias and books written by sages and scientists in different ages (Figure 1) (9).

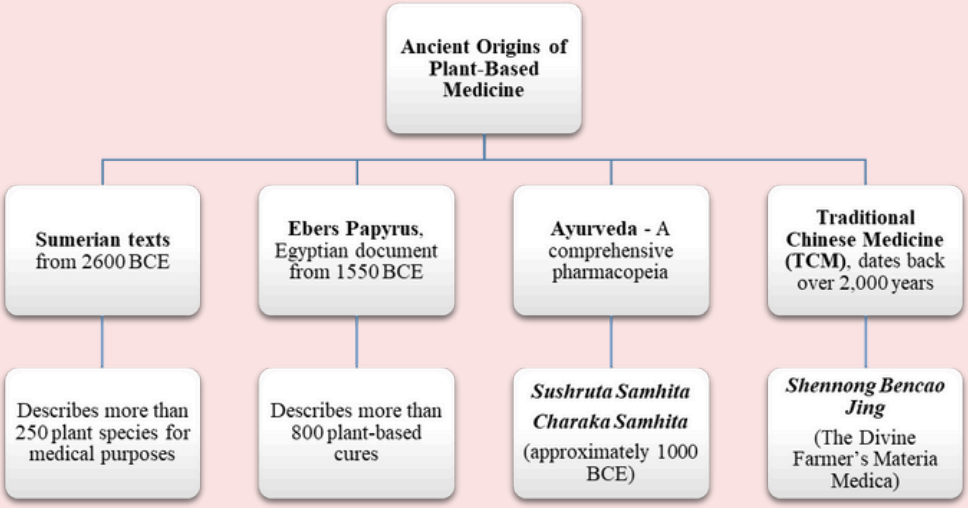

Figure 1. Evidences of use of plants in ancient ages

4.2. 18th to 20th century

In-depth treatises like *The Canon of Medicine* were written in 18th century. When botanists and early chemists started separating active ingredients from plants in the 18th and 19th centuries, empirical knowledge gave way to more methodical scientific investigation (Figure 2) (10). The government agencies in India, such as the Ministry of AYUSH, were created to encourage the incorporation of conventional plant-based remedies with scientific verification, setting standards for quality assurance and research (11).

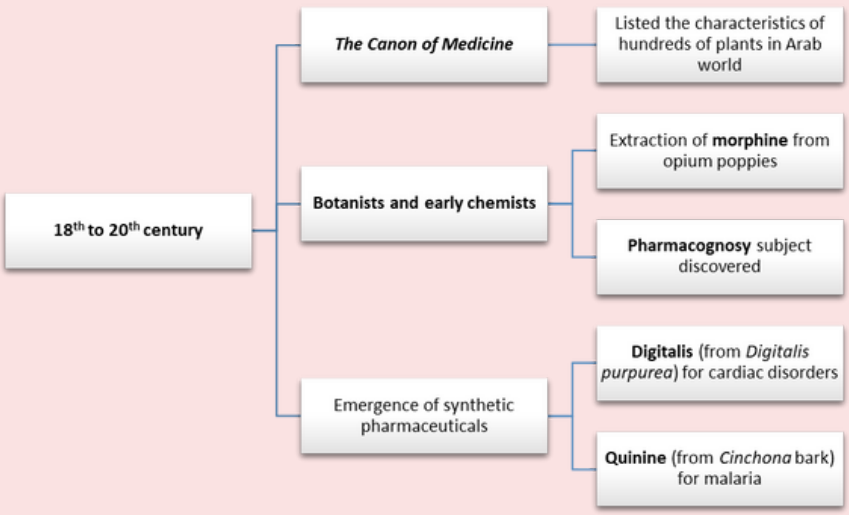

Figure 2. Advancements in herbal knowledge in 18th to 20th century

4.3. 21st century developments

Researchers are now able to discover and separate bioactive chemicals from plants, confirm their mechanisms of action, and create standardized formulations that satisfy global quality and safety requirements; which have been possible due to developments in biotechnology, molecular biology, and analytical chemistry (Table 1). The World Health Organization has acknowledged the importance of traditional plant-based remedies and has pushed for their inclusion in national healthcare systems as safe, scientifically proven alternatives (12).

Table 1. Isolated bioactive compounds from plants

Bioactive Compound	Plant Source
Alkaloid	
Piperine	*Piper sylvaticum* Roxb.
Berberine	*Berberis lycium* Royle
Lysergol	*Convolvulaceae* Juss.
Reserpine	*Rauvolfia serpentina* (L.) Benth. ex Kurz
Maculine	*Teclea afzelii* (Engl.)
Sanguinarine	*Chelidonium majus* L., *Sanguinaria canadensis* L., *Macleaya cordata* (Willd.) R. Br.
Chanoclavine	*Ipomoea muricata* (L.) Jacq.
Caffeine	*Camellia sinensis* (L.) Kuntze
Caranine	*Clivia miniata* (Lindl.) Verschaff.,*Crinum bulbispermum* (Burm.f.) Milne-Redh. & Schweick.
Evodiamine	*Evodia aromatica* (Sonn.) Pers.
Thalicfoetine	Roots of *Thalictrum foetidum* L.
Terpenes	
Eugenol	*Syzygium aromaticum* (L.), *Cinnamomum zeylanicum* Blume.
Cinnamaldehyde	*Cinnamomum verum* J. Presl.
Ursolic acid	*Salvia rosmarinus* Spenn., *Salvia officinalis* L.
Farnesol	*Vachellia farnesiana* (L.) Wight & Arn.
Carvacrol	*Thymus capitatus* (L.), *Thymus vulgaris* L.
Nerolidol	*Cannabis sativa* L.
Thymol	*Thymus capitatus* (L.)

Phenols	
Myricetin	*Myricaceae* Rich. ex Kunth., *Anacardiaceae* R.Br.,*Polygonaceae* Juss., *Pinaceae* Spreng. ex F.Rudolphi., *Primulaceae* Batsch ex Borkh.
Baicalein	*Thymus vulgaris* L., *Scutellaria baicalensis* Georgi,*Scutellaria lateriflora* L.
Epigallocatechin gallate	*Camellia sinensis* (L.) Kuntze
Chebulinic acid	*Terminalia chebula* Retz.
Emodin	*Rheum palmatum* L.
Curcumin	*Curcuma longa* L.
Quercetin	*Vitaceae* Juss., *Brassicaceae* Burnett,*Amaryllidaceae* J.St.-Hil., *Rutaceae* Juss.
Kaempferol	*Alpinia calcarata*
Resveratrol	*Vitis vinifera* L.
Apigenin	*Matricaria chamomilla* L.
Genistein	*Glycine max* (L.)
Organosulfur/isothiocyanate	
Allicin	*Allium sativum* L.
Ajoene	*Allium sativum* L.
Allyl isothiocyanates	*Armoracia rusticana*
Benzyl isothiocyanate	*Alliaria petiolata*
Berteroin	*Brassica oleracea* L.
Cheirolin	*Cheiranthus cheiri* L.
Alyssin	*Alyssum* L. sp.

5. Importance of integrating traditional and modern science

The development of phytopharmaceuticals as a reliable, efficient, and scientifically supported medical treatment depends significantly on the integration of ancient knowledge and modern science. Many advantages, such as improved efficacy, safety, and innovation in drug development, result from this synergy, which integrates the empirical knowledge of traditional methods with the accuracy of modern research. Knowing the importance of this integration helps to clarify how modern and traditional methods can work in collaboration to produce a more comprehensive healthcare paradigm.

5.1. Enhanced efficacy and safety

Evidence-based medicine is made possible by the application of modern scientific methods like pharmacology and bioassays, which enable researchers to verify and measure the effects of traditionally used botanicals. For example, research demonstrating the adaptogenic and anxiolytic properties of *Withania somnifera* (Ashwagandha) through the modulation of stress hormones like cortisol has confirmed its historic use in Ayurveda for stress reduction (13). Modern science can assure the constant quality of phytopharmaceuticals by combining traditional knowledge with regulated manufacturing procedures like GMP and verified extraction techniques. This is demonstrated by research on standardized *Panax ginseng* extracts, since stable ginsenoside levels in standardized products have been linked to dependable therapeutic effects in stress reduction, physical performance, immunological and cognitive processes, blood glucose and lipid management, and chronic obstructive pulmonary disease (14).

5.2. Improved understanding of mechanisms of action

The specific biological mechanisms of plants or their isolated compounds on particular health disorders are verified by current science, while traditional wisdom offers useful hints about which plants are effective for various ailments. For example, action of *curcumin* on particular inflammatory pathways has been linked to the anti-inflammatory properties of *Curcuma longa* which has long been used to treat digestive problems and joint pain because it suppresses nuclear factor-kappa B (NF-κB), a crucial regulator of inflammation (15).

5.3. Innovation in drug development

The extensive plant-based knowledge for isolation of bioactive compounds can serve as a basis for novel drug development breakthroughs. For instance, the discovery of the antimalarial medicine artemisinin, which is derived from *Artemisia annua* and it resulted in one of the most successful therapies for malaria and earned Dr. Tu Youyou a Nobel Prize in 2015 (16). More potent and bioavailable phytopharmaceuticals have been produced by combining conventional methods with cutting-edge formulation technologies. When taken in their raw form, turmeric and its active constituent *curcumin* are poorly absorbed; however, their bioavailability and therapeutic efficiency have been greatly enhanced by new formulations including liposomal curcumin and curcumin nanoparticles (17).

5.4. Sustainability and biodiversity conservation

To avoid overexploitation, traditional knowledge systems support ethical and sustainable harvesting methods like selective collecting and alternating harvest cycles. The Convention on Biological Diversity (CBD) and the World Health Organization (WHO) both acknowledge that incorporating traditional practices into conservation plans can be extremely important for preserving biodiversity and enhancing the phytopharmaceutical sector. Research and development partnerships with indigenous communities give these groups the chance to preserve their cultural tradition while gaining economic benefits (2).

5.5. Addressing global health challenges

Phytopharmaceuticals provide beneficial remedies that can supplement traditional treatments in facing the challenges of growing global health difficulties such antibiotic resistance, chronic illnesses, and mental health disorders. Certain phytopharmaceuticals have demonstrated potential as substitutes for traditional antibiotics, which are becoming more and more problematic because of germ resistance. Phytopharmaceuticals may offer new ways to treat resistant bacterial strains, according to research on plant-derived antimicrobials, such as the usage of neem and tea tree oil extracts. Plant-based substances that have shown promise in treating inflammatory ailments, cardiovascular diseases, and metabolic disorders include resveratrol, berberine, and gingerol (18).

The modern phytopharmaceutical sector demonstrates the applicability and flexibility of traditional medicine in contemporary healthcare by integrating ancient knowledge with state-of-the-art science. This forms the basis of how phytopharmaceuticals may promote sustainability and cultural preservation while addressing urgent global health concerns like chronic illnesses, antibiotic resistance, and mental health disorders.

6. Conclusion

In conclusion, India is well positioned to lead the global phytopharmaceutical market due to its sophisticated pharmaceutical sector and plenty of traditional medical expertise. India can produce safe, standardized plant-based medications that satisfy international standards by integrating traditional knowledge with modern science. India has more opportunity to innovate in this area with the help of supportive legislation, a robust export network, and growing demand for alternative medicines. This evolution of phytopharmaceuticals from traditional roots to a scientifically grounded industry not only drives economic growth but also reinforces India's position as a central player in advancing global health through natural and plant-based solutions. Regulatory compliance guarantees the safety and effectiveness of phytopharmaceuticals, which increases their adoption in mainstream healthcare

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Plant to phytopharmaceutical: The journey and future directions

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Abstract

Nature has an answer for all human needs. Since the beginning of human life, plants have been used as medicines, and these continue to be a valuable reservoir of therapeutic agents and pharmaceutical products. The journey of a plant from nature to the market involves selection, collection, authentication, extraction or isolation of bioactives, chemoprofiling, biological evaluation, and quality assurance. This article highlights the importance of each step and emphasises the need for a sustainable use of plants and incorporating new technologies in order to ensure a regular supply as well as quality, efficacy, and safety of plant products and phytopharmaceuticals.

Keywords: medicinal plants, phytopharmaceuticals, sustainable use, upgrading technology

1. Introduction

Nature has an answer for all human needs: clean air, food, shelter (timber), clothing (fibres), flavours, fragrances, and medicines. Since the beginning of human life, human beings have turned to nature to satisfy all needs. Plants have been used for nutrition and as medicines, and these continue to be a valuable reservoir of therapeutic agents and pharmaceutical products. People use different systems of medicines across the globe (Figure 1). In all systems of medicines, plants are an important reservoir of medicinal products as well as pharmaceutical aids.

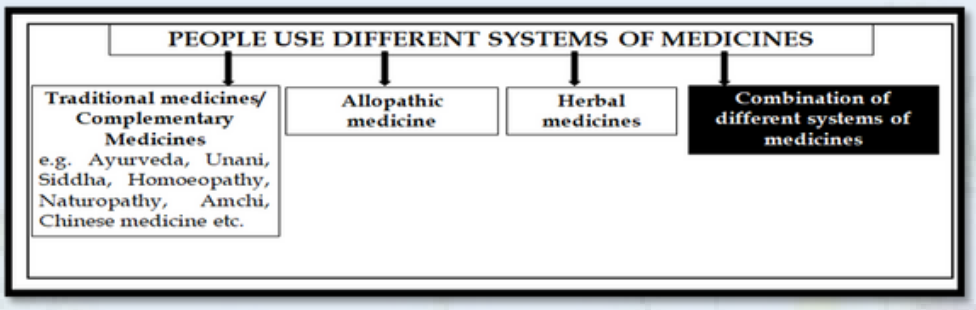


Figure 1. Different systems of medicine

Natural products (and their derivatives and analogues) represent over 50% of all drugs in clinical use in modern medicine. The World Health Organisation estimates that 80% of the people in developing countries of the world rely on traditional medicine for their primary health care, and about 85% of traditional medicine involves the use of plants or plant extracts. This means that more than 4 billion people in the world rely on medicinal plants as sources of drugs (1).

In the world of medicine, natural products are popular as:

- Pharmaceutical products (Therapeutic agents, Pharmaceutical aids, Models for drug discovery, For semi-synthesis of important drugs)
- Nutraceuticals
- Cosmetics/ cosmeceuticals
- Bio-pesticides
- Ethno-veterinary products

Plant-based traditional medicines, complementary therapies, and herbal medicines are extremely popular, not only in the developing countries but also in the 'developed nations', especially for chronic ailments. It is pertinent to mention that the world-wide trade of medicinal plants has been growing exponentially with an annual growth rate of 15%; it is likely to touch a scale of five trillion US dollars by 2050. The importance of plants in pharmacy cannot be overemphasised. Hence, it is imperative to understand the journey of a plant to a commercial product.

2. Journey of a plant to a phytopharmaceutical product: The steps

Plants are used in various forms and commercially a variety of formulations containing medicinal plants/ products are available commercially. The marketed preparations used in different systems of medicine contain plants or plant extracts or isolated phytoconstituents (figure 2). In layperson's words, these are phytopharmaceuticals medicines or therapeutic products obtained from plants and plant products.

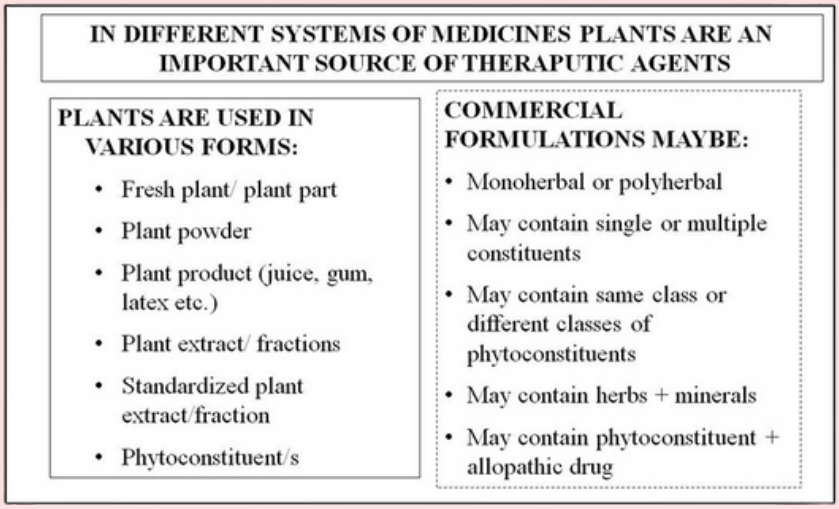


Figure 2. Different forms in which plants are used in various systems of medicine

As per the Drugs & Cosmetics (D&C) Rules, 1945, "Phytopharmaceutical drug" includes a purified and standard fraction with defined minimum four markers (bioactive or analytical that are determined qualitatively and quantitatively) in an extract of a medicinal plant or its part for internal or external use of human beings or animals for diagnosis, treatment, mitigation, or prevention of any disease or disorder, but does not include administration by parenteral route (2). For developing reliable a phytopharmaceutical product, correct identity, purity, quality, efficacy, safety stability must be determined (3). The overview of the steps involved in developing a commercial plant product in figure 3 (4).

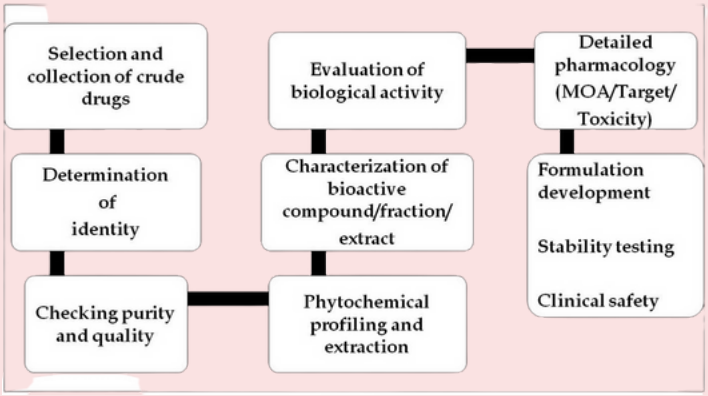


Figure 3. Steps involved in developing a commercial plant product

The steps for developing a plant product are discussed below:

2.1. Selection of plant

The rationale for selection of a plant must be clearly stated. The selection maybe ethno-guided based on traditional uses, based on field observations, chemotaxonomy driven, and based on type of reported phytoconstituents.

2.2. Procurement/collection of selected plant

Medicinal plants are procured from wild or cultivated sources. These have their advantages and limitations (Figure 3). In our country about 6,000-7,000 species are used in Indian systems of medicine and folk medicines. Of 960 species in trade, 178 species have an annual consumption > 100 MT. Only about 20% of these are obtained by cultivation (5).

	WILD SOURCES	CULTIVATED SOURCES
ADVANTAGES	•Easy access •Wide variety •Higher amount of secondary metabolites	•Regular supply •Greater uniformity •Known quality
LIMITATIONS	○Incorrect identification ○VARIATION ○NO REGULAR SUPPLY ○INDISCRIMNATE UTILIZATION (plants become vulnerable, threatened, endangered, extinct)	○More expensive ○Agrotechnology for large majority of Medicinal plants needs to be developed ○Knowledge transfer from research institutes is required. (Farmers reluctant to leave cultivation of known crops)

Figure 3. Advantages and limitations of wild and cultivated sources of crude drugs

Collection of raw material may be done from either source and to ensure reproducibility the place of collection-wild or cultivated, time/month and year of collection, plant part collected, method for drying (natural/artificial) must be documented. For standardization studies the plant should be collected from different geographical regions in different seasons and the various parameters should be examined.

2.3. Authentication of the collected material

For any industry, selecting the right raw material is the key to the process of making a quality product. In the journey of developing a phytopharmaceutical, authentication i.e. determination of the correct identity of the plant of interest is critical. If the plant material is wrong the entire process will be wasted (Figure 4).

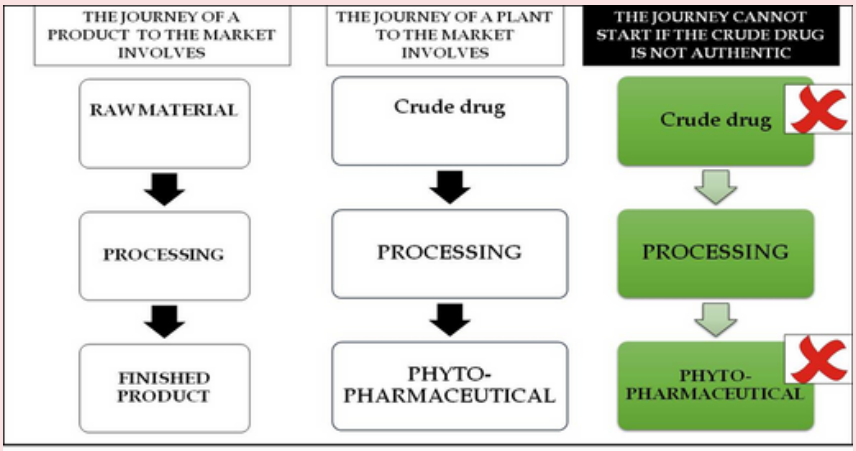


Figure 4. The importance of authentication of plants in herbal drug industry

Authenticating the plants may be done by taxonomists (especially for plants for which information is not available) or by studying the organoleptic features, microscopic features (including transverse section, powder microscopy and histochemistry and quantitative determination), physicochemical parameters of the plant (including foreign organic matter, moisture content, ash values, extractive

values swelling index, pesticide residues, microbial contamination, presence of heavy metals etc.). These results are compared with available literature to confirm the identity.

2.4. Preparation of extracts

Plants contain diverse constituents - primary and secondary metabolites as well as active and inert materials. The objective of preparing a plant extract is to separate the phytoconstituents which are responsible for the plant's activity. Figure 5 summarizes the general sequence employed for extraction.

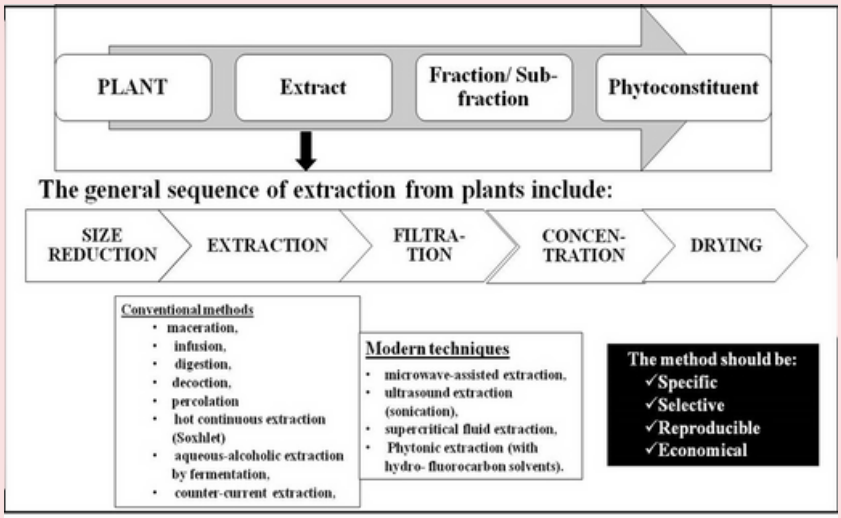


Figure 5. General sequence for preparing plant extract

To ensure reproducibility the method of size reduction of plant material, amount of plant material, crude drug : solvent ratio, and method of extraction should be recorded. Extraction should be exhaustive and for a new investigation it is preferable to prepare sequential extracts i.e. starting from non-polar going to medium polar and polar solvents. Method of extraction, duration of extraction and the conditions during extraction should be documented. For example: Maceration with methanol: water (80:20) for 7 days. Solvent replaced after every 48hours; in a shaking incubator at 37°C at 100RPM. At the end of 7 days the extracts to be pooled and concentrated under vacuum.

This is followed by phytochemical screening of the prepared extracts and quantification of the major/ target phytoconstituents (e.g. total alkaloid content; total flavonoid content) along with development of their TLC profiles. Subsequently fractionation of extracts (by solvent partitioning and /or chromatography) is done with a view to isolate bioactive fraction / constituent. Each step for fractionation/isolation should be recorded with all conditions. After that phytochemical profiling and chromatographic fingerprinting of fractions/sub-fractions and characterisation of isolated constituent/s is necessary.

2.5. Once the extracts are ready the question is: WHAT TO DO NEXT?

For pharmacognosists there are a number of options available. Most frequently two approaches are used in Figure 6.

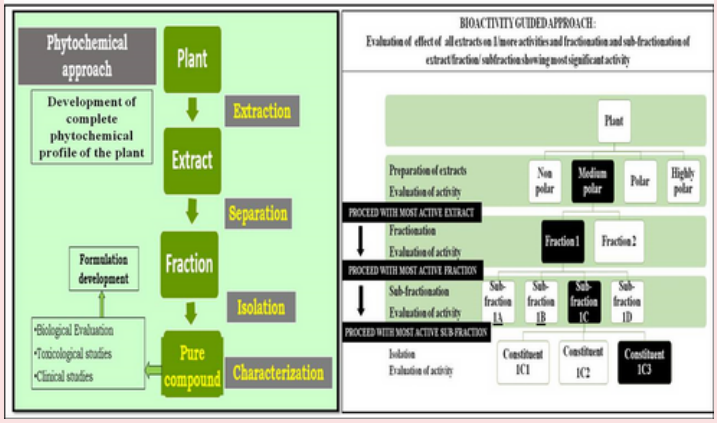


Figure 6. Different approaches to study plants

- **Phytochemical study of test extracts:** This involves separation, characterization and quantification of all secondary metabolites with a view to develop an exhaustive chemo-profile of the plant. This is followed by evaluation of bioactivity.
- **Bioactivity guided study of test extracts:** In this approach for studying plants the focus is on a particular activity. Various extracts are prepared and this is followed by evaluation of effect of all extracts on 1/more activities and fractionation and sub-fractionation of extract/fraction/sub-fraction showing most significant activity. The most active extract/ fraction/constituent is then chemo-profiled/characterized.

It is necessary to mention that in plants a particular activity may be due to one phytoconstituent or due to synergistic effect of a number of constituents. Thus while examining a plant one should understand that the bioactive component may be a single compound or a fraction or an extract.

2.6. Biological evaluation of the prepared extracts

The selected plant may have support of traditional literature or maybe used in folklore medicine; some plants may have preliminary pharmacological proof and some may have no evidence at all. Hence they have to be examined accordingly (Figure 7).

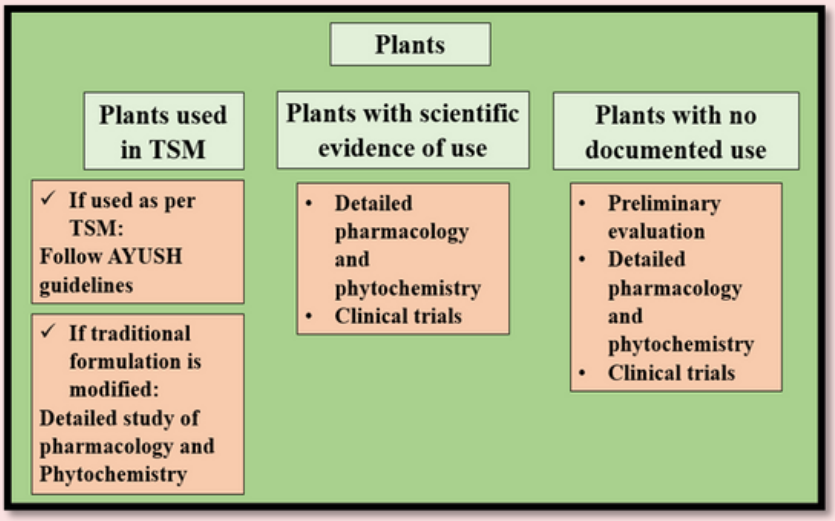


Figure 7. Pharmacological evaluation of plants

The general biological studies involve the following:

- Preliminary evaluation - selection of suitable in-vitro/ ex-vivo / in-vivo experimental model to evaluate the effect of the extracts and establish efficacy.
- Detailed pharmacological study to confirm the activity, study the mechanism of action and dose determination.
- Toxicity studies (as per OECD guidelines) - To determine the acute toxicity, sub chronic toxicity, and chronic toxicity

Then suitable formulations (according to allopathic, traditional or herbal medicine specifications) are made and commercialized.

3. Future directions

The journey seems easily doable but each step faces a number of challenges. Figure 8 highlights major constraints during the development of a phytopharmaceutical product.

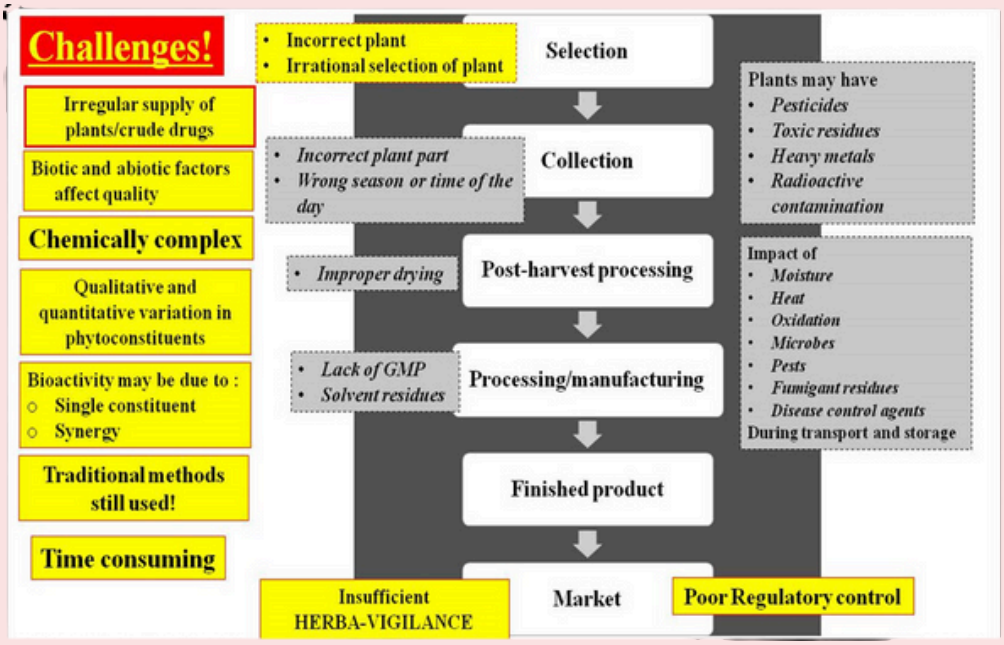


Figure 8. Challenges during the development of a phytopharmaceutical product

To overcome these challenges, figure 9 emphasises the type of testing that is essential for the raw materials (i.e. crude drugs), validation of the methods used for processing the plants and the tests that are required for evaluation of finished products (i.e. phytopharmaceutical products) (4,6).

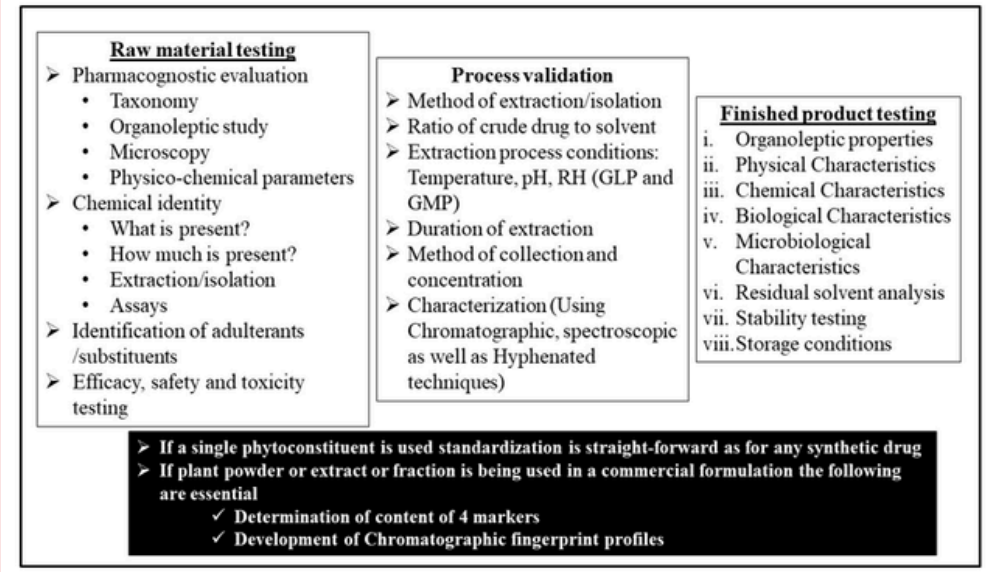
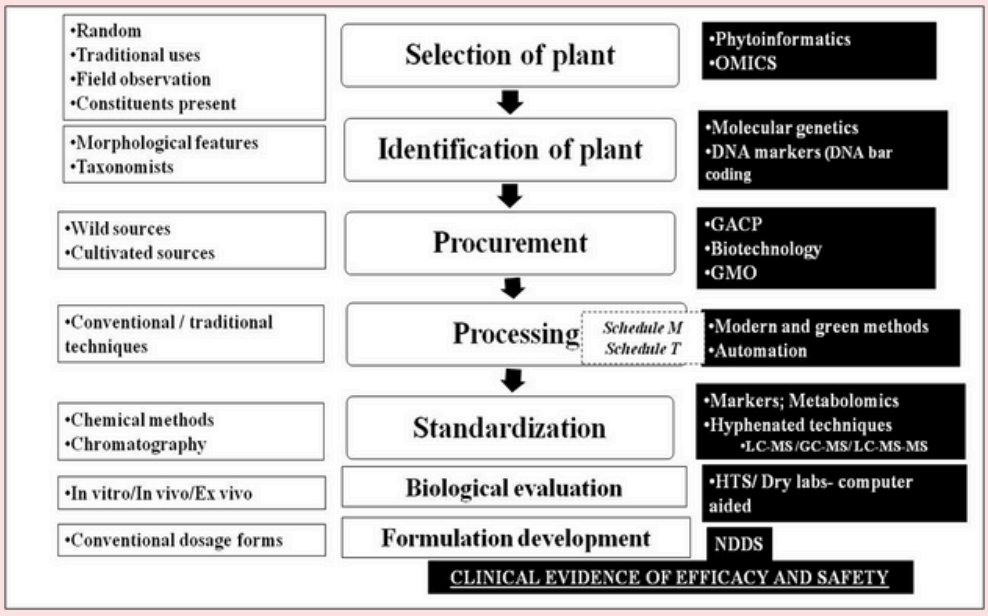


Figure 9. Testing for the development of a phytopharmaceutical product

The major objectives are to ensure a regular supply of good quality raw material (crude drugs) and to develop methods that are more specific and sensitive, faster, automated, reproducible, and cost effective.

Thus there is need to update and upgrade the steps involved. Figure 10 summarizes on what is being done and what should be included to assure that phytopharmaceutical products are of reproducible chemical purity and have reliable effectiveness and safety.



(GACP- Good agricultural and collection practices; GMO- genetically modified organisms; HTS- High throughput screening; NDDS- new drug delivery systems)

Figure 10. Current and newer methods for developing phytopharmaceutical products from plants

4. Conclusion

The key takeaways while working with plants are focus on sustainable use of plants and conservation of the environment. Along with development of commercial products with newer and faster techniques to generate detailed phytochemical profile and evidence of efficacy and safety thus leading to rational phytopharmaceutical product development.

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Ethnobotanical knowledge and its role in the development of Indian phytopharmaceuticals




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Abstract

This review deals with the crucial crossing of ethnobotanical knowledge and the development of phytopharmaceuticals in India, throwing into light the rich tapestry of traditional medicinal practices and the contributions that these have made toward modern drug discovery. India, with its biodiversity and a long history of the use of medicinal plants, has undergone some notable developments in research studies on phytopharmaceuticals, the best examples being Bacoside from *Bacopa monnieri,* Curcumin from *Curcuma longa,* and Artemisinin from *Artemisia annua*. Despite this promising potential, ethnobotanical knowledge faces challenges in the nature of biopiracy, loss of traditional practices, and a call for proper standardization in practice. Ethnobotany is definitely set for an upward trend and expansion in the near future, driven as it will be by continual advances in biotechnology, scope for joint collaboration between traditional healers and modern science, and supportive policies and institutional frameworks. Using ancient knowledge with modern scientific methods, India will be able to ensure future research that contributes toward developing better phytopharmaceuticals and hence, to health globally, while saving its rich cultural heritage.

Keywords: Phytopharmaceuticals, standardization, Ethnobotany, Artemisinin, Curcumin

1. Introduction

Ethnobotany is the science of the relationship between humans and plants, such as how cultures might interpret and utilize plants in their everyday lives. It has characteristics that belong both to botany (the science of plants) and anthropology (the study of human cultures) in regards to the usage of plants in medicine, food, ritual, clothing, shelter, etc., of human cultural practices (1). Ethnobotany deals with indigenous knowledge as well as the ways in which traditional societies have been using plants for centuries. Most importantly, this knowledge had mostly been communicated orally throughout generations that is to say it had a deep understanding of local species of plants and their applications. Its major area of study includes medicinal plants (2). Indeed, it stands on common knowledge that many modern pharmaceuticals have been derived from plants which have been long used by indigenous cultures to treat ailments. Plants often receive symbolic or religious functions within many societies. Ethnobotany is actually famous for focusing on the ways through which plants

are being interfaced into rituals and ceremonies, including spiritual beliefs (3). The ways through which plants are cultivated as sources of food, traditional ways of farming, plant domestication, and dietary practices are considered. Ethnobotany also looks into how such traditional knowledge can help in sustainable practice, conservation, and new agricultural or pharmaceutical products development (4).

2. The importance of ethnobotanical knowledge in drug discovery

Ethnobotanical knowledge is an important drug discovery tool since it includes the traditional uses of plants used by locals for medicinal purposes. Much bioactivity has been led from this ethnobotanical knowledge, which forms a good starting point for developing lead compounds into useful drugs. The link between indigenous knowledge and modern science has led to many life-saving drugs. Many new treatments are still being discovered today through this important pathway. Several reasons account for why ethnobotanical knowledge is important in drug discovery (4).

2.1. Source of bioactive compounds

Ethnobotanical knowledge, naturally, delineates plants that, over many centuries, have been used by traditional healers to treat a variety of medical conditions. Such plants may contain bioactive compounds that could be isolated and studied for their therapeutic effects (5). For instance, one of the very earliest examples of ethnobotany contributing to drug development was the isolation of salicylic acid from the bark of Salix species willow trees, which has been used for centuries in traditional medicine to relieve pain and inflammation (6).

2.2. New drug discovery

Most medicines of modern chemical synthesis trace their roots to ethnobotanical knowledge. For instance, quinine cures malaria in medicine. It had been obtained from the bark of the cinchona tree, (*Cinchona officinalis)* used by indigenous South American peoples for the treatment of fever (7). Paclitaxel is one of the most important drugs in cancer therapy and was isolated from the Pacific yew tree *Taxus brevifolia* based on studies of Native American medicinal practices (8). Artemisinin is the contemporary prototype of malaria drugs, obtained from the use of the sweet wormwood plant known as *Artemisia annua* in Traditional Chinese Medicine (9).

2.3. Preservation of traditional knowledge

There are abundant sources of indigenous and local knowledge systems regarding the biodiversity of plants as well as their potential medicinal properties. Recording and preserving such knowledge becomes significant since rapid urbanization, environmental degradation, and cultural changes face a threat to their annihilation (10). The ethnobotanical research thus acts as a bridge between practice and modern science to prevent the loss of valuable medicinal plants and knowledge (11).

2.4. Addressing emerging diseases

Ethnobotanical research may therefore hold solutions to modern medical challenges, such as antibiotic resistance and emerging infectious diseases. It may hold clues to natural products with antimicrobial properties, which are increasingly important because pathogens are evolving resistance to synthetic drugs (12). These include the study of indigenous remedies for plants that are currently used in traditional medicine as a source of knowledge for novel or alternative antibiotics because some traditional antibiotics have been failing while causative agents remain susceptible (13).

3. Ethnobotanical knowledge in India: An overview

3.1. India’s biodiversity and medicinal plant wealth

India stands at the top of the list of most biodiverse countries in the world, with incredible richness in diversity across a variety of different ecosystems, harbouring high ranges of plant species. This biodiversity has taken India's medicinal plants as treasure houses; many of them are integral to traditional medicine systems. It has more than 8,000 species of medicinal plants that have been used to treat a wide variety of ailments over centuries. Such plants, typically found in forests, grasslands, and mountainous regions, provide the foundation of both traditional remedies and today's

phytopharmaceutical research. The fact that so many medicinal plants have been found in India emphasizes the importance of preserving the country's biodiversity for future pharmaceutical discovery (14).

3.2. Indigenous communities and their traditional knowledge systems

These people are the original Indians who are deeply entwined with natural surroundings. These sections of Indian society mainly depend on these medicinal plants for their health needs. In general, each of these communities has ethnobotanical knowledge of a profound nature spanning generations, beginning with treatment in cases of illness to religious ceremonials and general life (15,16). The knowledge is localized as specific to the flora of a region and involves complex understanding of plant properties, preparation techniques, and application. It becomes significant to preserve this traditional knowledge for its worth in cultural heritage but also for its possible contribution to modern medicine (3).

3.3. Role of Ayurveda, Siddha, and Unani Systems in ethnobotany

India has traditional healing systems, which include Ayurveda, Siddha, and Unani. Ayurveda dates back over 3,000 years ago when the early people were using an array of herbs and plants aimed at balancing the body's systems and the treatment of diseases (17). The Siddha system, primarily practiced in South India, places significant emphasis on minerals and plants. The Unani medicines the Arabs introduced involve plant medicine based on Greco-Arabic medicine (18). Moreover, these systems provide health care to millions of people and contribute to ethnobotanical research since they highly emphasize the medicinal properties of India's rich plant biodiversity.

4. Ethnobotany and modern phytopharmaceutical development

4.1. Process of translating traditional knowledge into modern medicine

The process of translating ethnobotanical knowledge into modern medicine involves several stages starting with the documentation of traditional uses of plants by indigenous communities and traditional healers. Researchers identify plants with promising medicinal properties and conduct preliminary studies to isolate bioactive compounds (19). These compounds are then subjected to rigorous scientific analysis, including laboratory testing, chemical analysis, and pharmacological studies. After initial identification, clinical trials are conducted to assess the efficacy and safety of the compounds (20). This process, which merges traditional wisdom with modern science, often leads to the development of new phytopharmaceuticals that can be mass-produced for global healthcare markets.

4.2. Examples of Indian medicinal plants in phytopharmaceutical development

The rich biodiversity of Indian medicinal plants has been instrumental in the development of phytopharmaceuticals. Numerous studies have highlighted their therapeutic and pharmacological efficacy, emphasizing various plants' potential roles in contemporary medicine (21). For instance, Murugan Prasathkumar (2021) discusses several Indian medicinal plants known for their antimicrobial, antioxidant, anti-diabetic, and anti-cancer properties. These characteristics underline the importance of these plants as sources for new drug formulations and therapies (22). The integration of traditional knowledge with modern scientific research can lead to significant advancements in drug discovery.

Furthermore, the ongoing research into Indian medicinal formulations demonstrates their relevance in addressing current health challenges, such as the COVID-19 pandemic. Salim Anisha (2021) notes that traditional medicines may have contributed to India's relatively low COVID-19 mortality rate by providing antiviral and immunomodulatory effects (23). This highlights the necessity for rigorous clinical trials and investigations into these plants to validate their efficacy and safety for broader applications (24). The IMPPAT database serves as a crucial resource in this context by cataloging over 1,700 Indian medicinal plants along with nearly 10,000 phytochemicals. By identifying potential druggable compounds that are distinct from existing FDA-approved drugs, this database aids researchers in discovering novel therapeutic agents derived from natural sources (25). Overall,

the intersection of traditional practices and modern pharmacological research underscores the significance of Indian medicinal plants in phytopharmaceutical development.

5. Key medicinal plants in India's ethnobotanical tradition

India's ethnobotanical legacy encompasses numerous important medicinal plants that have been in use for thousands of years in ancient systems of healing, including Ayurveda, Siddha, and Unani. Neem (*Azadirachta indica)* is among the most commonly used medicines against different skin disorders and infections by virtue of its antimicrobial and anti-inflammatory properties (26). In many Indian homes, Tulsi, an immunostimulant with supposed respiratory health benefits, is considered a precious plant. Ashwagandha (*Withania somnifera*) is an adaptogenic herb known for managing stress and energizing. One of the most known anti-inflammatory agents and antioxidants, in addition to diseases involving joint pain and digestive health, is that of turmeric, consisting of a compound known as curcumin (27). Amla (*Phyllanthus emblica*) is a herb rich with vitamin C, very rejuvenating in Ayurveda, which boosts immunity and brings about long life. These plants not only play the role of culture and spiritual entities but are also currently under research in modern phytopharmaceutical research for the much-extensive medicinal potential associated with them (Table 1).

Table 1. Some herbal drugs used in the pharmaceutical industry

Plant Name	Scientific Name	Traditional Uses	Key Bioactive Compounds	Modern Applications	Ref
Neem	*Azadirachta indica*	Antimicrobial, anti-inflammatory, skin ailments	Azadirachtin, Nimbin	Antibacterial, antifungal, skin care, dental hygiene	(28)
Tulsi (Holy Basil)	*Ocimum sanctum*	Immunity booster, respiratory issues, stress relief	Eugenol, Ursolic acid	Immune support, respiratory health, adaptogen	(29)
Ashwagandha	*Withania somnifera*	Stress relief, vitality, memory enhancement	Withanolides, Alkaloids	Adaptogen, stress management, cognitive support	(30)
Turmeric	*Curcuma longa*	Anti-inflammatory, digestive health, wound healing	Curcumin	Anti-inflammatory, antioxidant, joint health, cancer research	(31)
Amla (Indian Gooseberry)	*Phyllanthus emblica*	Rejuvenation, immunity booster, digestive tonic	Ascorbic acid (Vitamin C), Gallic acid	Antioxidant, immune support, anti-aging, digestive aid	(32)
Brahmi	*Bacopa monnieri*	Memory enhancer, anxiety relief, cognitive health	Bacosides	Nootropic, memory support, cognitive health	(33)
Shatavari	*Asparagus racemosus*	Reproductive health, lactation support, hormone balance	Saponins, Asparagamine A	Women's health, fertility, hormonal balance	(34)
Guggul	*Commiphora wightii*	Joint pain relief, cholesterol regulation, arthritis	Guggulsterone	Anti-inflammatory, cholesterol-lowering, arthritis support	(35)
Giloy (Guduchi)	*Tinospora cordifolia*	Fever, immune support, liver protection	Tinosporine, Cordifolioside	Immunomodulator, antipyretic, liver protection	(36)
Arjuna	*Terminalia arjuna*	Cardiovascular health, wound healing, respiratory health	Arjunic acid, Tannins	Heart health, antioxidant, blood pressure regulation	(37)

6 Challenges in utilizing ethnobotanical knowledge for drug development

6.1. Biopiracy and Intellectual Property Rights (IPR) issues

Biopiracy is a term used to describe the unauthorized use, exploitation, or extraction of biological resources like plants, animals, and traditional knowledge from indigenous communities or developing countries by individuals or organizations for commercial gain. This unethical practice raises serious concerns about the protection of intellectual property rights (IPR) and the rights of indigenous communities. One of the major issues with biopiracy is the exploitation of traditional knowledge and resources without obtaining proper consent or providing fair compensation to the communities that have developed and preserved this knowledge for generations. In many cases, indigenous communities are not aware of the value of their resources or are coerced into signing unfair agreements that do not adequately protect their rights. Another problem is the lack of legal frameworks and enforcement mechanisms to prevent biopiracy and protect the intellectual property rights of indigenous communities.

Many countries do not have strong laws in place to regulate the collection, use, and commercialization of biological resources, making it easy for companies to exploit these resources without facing any consequences. Furthermore, biopiracy can have negative consequences for biodiversity and the environment. When plants and animals are removed from their natural habitats without proper regulation, it can disrupt ecosystems and endanger species that are already under threat from climate change, deforestation, and pollution. To address these issues, it is important for countries to strengthen their legal frameworks and enforce strict regulations to prevent biopiracy and protect the intellectual property rights of indigenous communities. Companies and researchers should also engage in ethical practices and seek informed consent from communities before extracting biological resources or traditional knowledge. In conclusion, biopiracy is a serious issue that highlights the need for stronger laws and enforcement mechanisms to protect the intellectual property rights of indigenous communities and prevent the exploitation of biological resources for commercial gain. As a result, local communities will be left without patent or reward for these natural compounds derived from their traditional practices. Poor IPR frameworks in most countries exacerbate this problem, and indigenous peoples cannot enjoy protection over their knowledge base and resources (38). Ethical drug development needs fair benefit-sharing mechanisms and the acknowledgment of contributions by traditional healers and communities.

6.2. Loss of traditional knowledge due to modernization and cultural erosion

The new challenge facing preservation of traditional ethnobotanical knowledge is a quicker tempo of modernization. All together, these factors slowly draw the transmission of traditional practices to the younger generations (39). Time and modern healthcare systems put an end to a rich source of knowledge regarding local plants and their uses within communities. This cultural erosion not only threatens the survival of such traditional practices but also undermines the possibility of finding new medicinal compounds, which can be beneficent to modern medicine (40). Efforts in recording and rejuvenating traditional knowledge are indispensable if this loss has to be averted and the indigenous communities' wisdom has to be tapped.

6.3. Standardization, quality control, and clinical validation of phytopharmaceuticals

There also remain issues on standardization, quality control, and clinical validation given the transition from traditional knowledge to modern phytopharmaceuticals. One big difference between synthetic drugs and plant-based medicines is that while the former is largely standardized, variability in the latter can be remarkably high by several factors, such as environmental conditions, cultivation practices, and processing methods (41). The sources of such variability are themselves safety and efficacy risks in clinical applications. Standardized protocols for harvesting, processing, and testing these medicinal plants have to be established for the sake of constant quality (42). Scientific validation through proper clinical trials also becomes indispensable for the safety and efficacy of such phytopharmaceuticals, which are very expensive in terms of cost and time-consuming (43). Overcoming the challenges will make ethnobotanical knowledge smoothly integrate into modern health systems.

7. Case studies of successful phytopharmaceuticals developed from ethnobotanical knowledge

Some repute phytopharmaceuticals have resulted from ethnobotanical knowledge; this goes to show that a wealth of information and experience exists in traditional treatments, something that could form a good base for modern medicine (44). Some of the notable success stories here are in Paclitaxel, a chemotherapy agent derived from the bark of the *Taxus brevifolia* tree, the Pacific yew. In native cultures, it has long been used to treat a variety of infections, but today it forms one of the cornerstones of treatment for ovarian and breast cancers (45). An interesting example is Artemisinin, a compound derived from *Artemisia annua*, which has been used traditionally in Chinese medicine for hundreds of years to treat fevers. The use of artemisinin-based therapies has gained dominance for the treatment of malaria around the world (46). Another compound Curcumin extracted from turmeric (*Curcuma longa*) has also attracted immense interest owing to its 'anti-inflammatory' and 'antioxidant' actions, and is now a substance added to dietary supplements and pharmaceutical preparations (Table 2). These case studies demonstrate how in the end, the combination of indigenous knowledge and scientific research leads to good treatments for everybody's health.

Table 2. Case studies of some drugs that are used in ethnobotanical system

Case Study	Plant Name	Scientific Name	Traditional Uses	Active Compounds	Development Process	Modern Applications	Global Impact	Ref
Development of Bacoside	Brahmi	*Bacopa monnieri*	Memory enhancement, cognitive support, anxiety relief	Bacosides	Isolated from the plant, followed by pharmacological studies and clinical trials	Memory enhancers, cognitive support supplements	Recognized as a nootropic; widely used in cognitive health products	(47)
Curcumin from Turmeric	Turmeric	*Curcuma longa*	Anti-inflammatory, antioxidant, digestive health	Curcumin	Extracted and purified; various studies on efficacy for inflammatory conditions	Dietary supplements, anti-inflammatory drugs, cancer research	Global use in dietary supplements; significant research into cancer and chronic disease management	(48)
Anti-malarial Drug from Artemisia annua	Sweet Wormwood	*Artemisia annua*	Treatment of fevers, traditional medicine for malaria	Artemisinin	Identified through ethnobotanical studies; developed as an anti-malarial drug	First-line treatment for malaria; artemisinin-based combination therapies (ACTs)	Major contribution to global malaria control efforts; has saved millions of lives	(49)

8. Conclusion

Integration of such ethnobotanical knowledge with the present focus on phytopharmacological subjects opens significant avenues for drug discovery and innovative healthcare in India. Such tremendous biodiversity and traditional medicinal practices make up an enormous reservoir of potential therapeutic agents, some of which are now successful case studies in Bacoside, Curcumin, and Artemisinin. So, knowing about the history of their development would go well beyond merely interesting reading. However, due to the existence of biopiracy, loss of traditional knowledge, and standardization requirements, the ethical considerations and the strong frameworks have to be established for research practices. Biotechnological advances can significantly add worth to

ethnobotanical research since interdisciplinary collaboration between traditional healers and scientists can flourish well, and policy supports are stronger. Valuing and preserving traditional knowledge while simultaneously drawing from the modern scientific approaches of the world, India can spearhead health solutions that not only remain sustainable and effective but are also locally relevant as well as applicable globally.

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Leveraging phytopharmaceuticals and nanocarriers for enhanced therapeutic outcomes


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Abstract
Although India has a vast heritage in traditional medicine, only a fraction has been scientifically explored for medicinal value, leaving a large area scientifically unexplored. Standardization of plant-based formulations, setting quality benchmarks, and ensuring sustainable harvesting practices are some crucial issues. Translating phytoactives into advanced delivery systems is still an evolving field. This review highlights the enhanced therapeutic outcomes of phytochemicals with nanocarriers that address their physicochemical and biopharmaceutical limitations and enabling targeted delivery. Additionally, it discusses pathways for India to position itself as a global leader in phytopharmaceuticals.

Keywords: Phytopharmaceuticals, Nanocarriers, National Medicinal Plants Board.

1. Introduction

Herbal medicines have been used as a primary source of medication for the treatment of numerous illnesses since the beginning of humanity. Traditional medical systems like Siddha, Unani, and old Ayurveda are widely used in India. Phytopharmaceuticals are medicines that are derived from plants and have shown great potential to cure the majority of diseases or disorders (1). A purified and standardized fraction derived from a medicinal plant or its specific parts is referred as phytopharmaceuticals. This fraction must contain at least four bioactive or phytochemical compounds, that have been qualitatively and quantitatively assessed. These drugs are intended for human or animal use, either internally or externally, for diagnosing, treating, mitigating, or preventing diseases or disorders (2). Phytopharmaceuticals are secondary plant metabolites that mainly include alkaloids, glycosides, tannins, terpenoids, and flavonoids. According to the WHO, greater than 80% of the population globally rely on herbal medicines as a source of primary treatment (3).

Botanical research proposed that there are around 3,50,000 different plant species in the world but only 35,000 different species are exploited for the treatment of several illnesses. As reported, merely 15% of medicinal products have undergone thorough qualitative and quantitative phytochemical analysis while, only 6% are screened biologically. The remaining plants have been largely overlooked, suggesting that this approach holds significant promise for developing new, more effective medicinal agents. According to a report by Rajat Nath and co-workers, there is progressive growth of herbal industries producing phytopharmaceuticals worldwide with 18 billion dollars in 2005, 83 billion dollars in 2019, and it is expected to be 550 billion dollars in 2030 (4). India exports approximately 32,000 tonnes of herbs annually, while China leads as the world's largest producer of herbal products, exporting around 120,000 tonnes each year

The phytopharmaceuticals market is valued at approximately $15.23 billion. According to Data Bridge Market Research, the phytomedicines and herbal extracts sector was worth $8.26 billion in 2021 and is projected to grow to $15.23 billion by 2029, with a compound annual growth rate (CAGR) of 7.95% from 2022 to 2029.The market for plant extracts has expanded significantly in the last several years. It will grow from USD 27.94 billion in 2023 to USD 30.55 billion in 2024 at 9.4 % compound annual growth rate (CAGR) (5).

2. Nanocarriers for enhanced therapeutic outcomes of phytopharmaceuticals

Despite their enormous potential as therapeutic agents, phytochemicals have various shortcomings, like poor solubility and bioavailability, high dose, narrow therapeutic index etc. Because of these physicochemical and biopharmaceutical issues, effective drug delivery systems involving phytochemicals are scarce. Polyphenols like curcumin, quercetin and Epigallocatechin gallate have poor solubility while quercetin is also susceptible to oxidative degradation, curcumin is unstable in physiological pH and epigallocatechin gallate has poor stability in neutral and alkaline pH. Flavonoids like rutin and naringenin have poor solubility and poor gastrointestinal absorption. Similarly, alkaloids like berberin, terpenoids and lutein have poor solubility and stability issues.

These limitations are often addressed by formulating the phytochemicals into nano-carriers (like liposomes, solid lipid nanoparticles, or nanoemulsions) (Figure 1), modifying their chemical structure, or using absorption enhancers such as piperine. Epigallocatechin gallate (EGCG), a polyphenol present in green tea, is beneficial in preventing and treating diabetes obesity, cancer and vascular diseases. It degrades quickly in the gastrointestinal environment and has a very low intestinal absorption. After drinking two cups of green tea, the oral bioavailability of epigallocatechin may be as low as 0.1%, with a peak plasma concentration of 0.15 μM. These factors make it impossible to get therapeutically adequate EGCG concentrations from natural sources. Nano-formulations are widely explored to produce therapeutically effective EGCG. In an investigation by Frias et al., EGCG was encapsulated in SLN and NLC containing Precirol as the solid lipid. High stability of EGCG was revealed in the simulated gastric and intestinal environment (6). Berberine (BER), an isoquinoline alkaloid extracted from Berberis vulgaris, has been used to treat various disorders, including cancer. However, its clinical use is restricted by its low solubility and limited bioavailability.

In a study BER-liposomes were created for anticancer activity against MKN-45 (gastric cancer cell line). Liposomes protected BER's antioxidant activity and improved its bioavailability. BER-loaded liposomes depicted significantly greater cytotoxic activity against MKN cell lines than free BER (7).

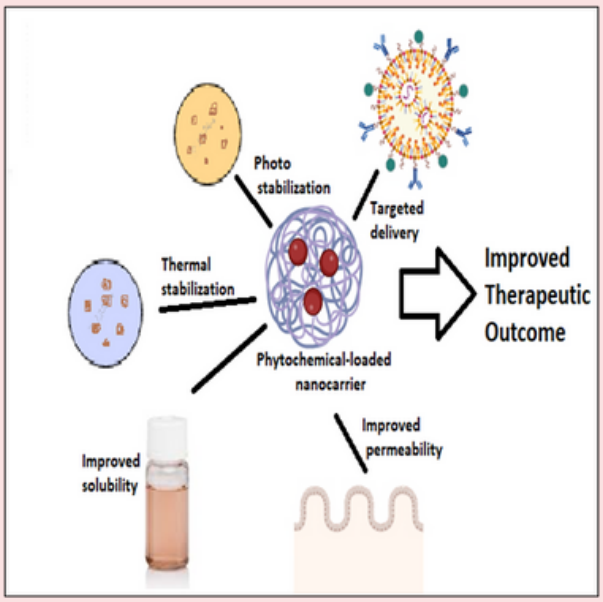

Figure 1. Functions of nanocarriers to improve therapeutic outcomes of phytopharmaceuticals

3. Key therapeutic applications of phytopharmaceutical nanocarriers

3.1. Neurodegenerative diseases

After Alzheimer's disease, Parkinson's disease (PD) is one of the most common age-related illnesses to be diagnosed. Neurodegenerative disorders (NDDs) are marked by a gradual decline in neuronal function, often leading to neuronal death. Key dysregulated signaling pathways such as protein misfolding, oxidative stress, inflammation, and apoptosis are central to the molecular mechanisms underlying neuronal damage. Introducing multi-target therapies via advanced systems that can cross the blood-brain barrier (BBB) could enable control over NDDs by modulating these pathways concurrently. Phytochemicals, known for their multi-target therapeutic effects, offer neuroprotection through diverse mechanisms.

Advancements in bio- and nanotechnology and the use of natural substances like ginseng, ginkgo biloba, and flavonoids as novel or supplementary treatments are gaining significant interest. In a study Guzman et al., loaded curcumin on human serum albumin nanoparticles for ameliorating PD features in the *C. elegans* model. Perhaps, Curcumin is poorly bioavailable but loading it on albumin nanoparticles increased its solubility by 255 folds and curcumin loaded nanoparticles were beneficial in protecting dopamine neurons preventing the development of symptoms resembling those of PD in a model system (8). Phytochemicals have shown potential effect in Alzheimer's disease. Resveratrol a polyphenol present in grapes depolymerize Aβ peptides through a proteasome function. However resveratrol is cleared vary rapidly from blood. Targeting it directly to the brain can enhance its therapeutic outcome markedly. NLC loaded resveratrol delivered intranasally was successful in delivering the drug to the brain and enhancing memory function in a preclinical study (9). Resveratrol, curcumin, quercetin, ginsenoside, naringenin, and retinoic acid nanoformulations have demonstrated beneficial benefits on stroke. These nanoformulations enhance the activity of superoxide dismutase, catalase, glutathione, and mitochondrial complex enzymes, thereby reducing oxidative stress and generating a therapeutic effect (10).

3.2. Targeted delivery of phytochemicals for cancer therapy

Phytochemicals can act as chemoprotective agents by regulating essential cellular processes, including DNA repair, apoptosis, cell proliferation, cell cycle, and metastasis. Recently, BSA nanoparticles (NPs) loaded with ginsenoside Rg5 were designed to enhance the therapeutic efficacy of Rg5 by targeted tumor delivery. Compared to free Rg5, NPs showed enhanced anticancer effectiveness in MCF-7 cells, likely due to improved uptake and increased cell death. In an in-vivo MCF-7 xenograft mouse model, folic acid-modified, Rg5-BSA NPs also achieved superior tumor growth suppression over free Rg5. Bioimaging analysis showed that these NPs had enhanced tumor-targeting abilities (11).

Additionally, green synthesis of metallic nanoparticles through the antioxidant effects of various phytoconstituents like flavonoids, amino acids, alkaloids, tannic acids, polyphenols, terpenoids, proteins, and sugars is gaining attention. Metal nanoparticles with anticancer potential can be synthesized phytogenically using a variety of plant sources. Examples of green-synthesized silver nanoparticles include those produced from the ethanol extract of *Artemisia tournefortiana* Rchb, leaf extracts of *Morus alba,* aqueous leaf extracts of *Annona muricata*, aqueous extracts of *Carissa carandas,* and extracts from L*eucophyllum frutescens* and *Russelia equisetiformis* (12).

3.3. Phytochemical-nanosystem for metabolic diseases

Metabolic disorders present major global health challenges, with metabolic syndrome contributing to a significant rise in type II diabetes and cardiovascular disease. Plant-based natural products offer insulin-sensitizing, anti-inflammatory, and antioxidant benefits with minimal side effects, making them appealing alternatives. Polyphenols, in particular, have been widely studied, with nanoencapsulation emerging as a promising approach to enhance their solubility, bioavailability, stability, and reduce toxicity.

One of the biggest clinical issues facing health, which is developing worldwide is metabolic diseases. Diabetes mellitus type II and cardiovascular illnesses have increased five and two folds, respectively, in recent years. Natural products, particularly plant extracts, are thought to be an alternative because of their minimal side effects and insulin-sensitizing, anti-inflammatory, and antioxidant qualities. Because of their many advantages, polyphenols have been thoroughly researched, and numerous methods have been developed to minimise their negative effects and maximise their positive effects. One possible technique to get around polyphenols' toxicity, low solubility, and decreased stability and bioavailability is nanoencapsulation. In an in vivo animal model of streptozotocin-induced diabetes, myricitrin solid lipid nanoparticles were efficient in treating both diabetes and hyperglycemia (13). In Brazil, copaiba oil, an oil-resin derived from an Amazonian tree, is used as a natural remedy. Copaiba oil is primarily composed of β-caryophyllene, a calcium channel blocker. It inhibits cell development and contains antioxidant and anti-inflammatory properties (14,15).

4. Phytochemical nanoformulations under clinical trials

In recent years, phytochemical nano-formulations have gained significant attention for their therapeutic capabilities; however, their effectiveness has mainly been demonstrated in preclinical studies. While a few have progressed to clinical trials, they have failed to get regulatory approval. Failure to advance beyond phase I, often due to the challenges with stability and bioavailability. More clinical trials will be crucial in bringing these phytochemical nanoparticles to the market. The only two approved nano-based phytochemical formulations are Paclitaxel Nanoparticles (Abraxane®), intended for metastatic breast cancer, pancreatic and non-small cell lung cancer, and Docetaxel Nanoparticles (Taxotere®), indicated for breast, non-small cell lung and prostate cancer. Docetaxel, a semi-synthetic paclitaxel derivative, is developed as a nanoparticle formulation to improve solubility and decrease hypersensitivity reactions.In a double-blind clinical trial, nano-micelle loaded with curcumin tested on 50 patients with metabolic syndrome revealed decreased malondialdehyde level and improved adiponectin level with overall increased total antioxidant capacity (16). Quercetin PEG-PLGA nanoparticles is in the phase 2 clinical trials against tongue squamous cell carcinoma. Reports of initial study revealed that it decreased cell viability and increased apoptotic rate (17).Resveratrol has been found to activate the Notch-1 protein, which can inhibit tumor cell growth. Resveratrol therapy would significantly increase Notch-1 activation in post-treatment biopsies of patients with low-grade GI neuroendocrine tumors compared to pretreatment levels (18).

5. Phyto-nanomedicine in the Indian pharmaceutical sector: The path forward

India, with its rich heritage in traditional medicine and an abundance of medicinal plant resources, is well-positioned to lead in the global phytopharmaceutical market. Here are some ways India can use to become a global leader in the field of phyto-nanomedicine.

5.1. Emphasis on targeted and advanced technologies

Escalating investment in targeted drug delivery research programs focused on developing phytopharmaceuticals loaded nanocarriers like phytosynthesized nanoparticles, liposomes, lipid nanoparticles etc. to improve the therapeutic outcome of these phytochemicals. Nanocarriers improve their physicochemical and biopharmaceutical properties and enable targeted delivery for diseases like cancer.

Also using High Through-Put Screening methods and AI based data analytics for rapidly identifying phytoactives from large reserve of plant extracts.

5.2. Developing regulatory framework to meet the international regulatory requirements

India’s regulatory framework is still evolving for phytopharmaceuticals. Establishing a harmonized guidelines to ensure safety, efficacy, quality and batch to batch consistency of phytopharmaceuticals, alongwith standardized methods and formulation protocol that ensures consistency and efficacy will help meet the international regulatory standards and facilitate smoother transformation from lab to market (19).

5.3. Indian government policy to foster phytopharmaceutical research in pharmaceutical industries

Government initiatives to provide funds for research on phyto-nanomedicine under the Ayushman Bharat Scheme will encourage companies to research in this field. Similarly, a collaboration of the National Medicinal Plants Board (NMPB) with pharmaceutical companies will boost phyto-nanomedicine ventures fostering the export of phytopharmaceuticals. With these initiatives, India can be branded as a credible source of effective and safe phytopharmaceuticals (20).

5.4. Enhancing Clinical Trials and real-world evidence

Establishing dedicated clinical trial institutions for phytopharmaceuticals in collaboration with research institutions and hospitals and escalating clinical trials is key for achieving regulatory approval. Emphasis should be placed on generating real-world evidence on efficacy and safety of phytopharmaceuticals, as well as the post-marketing surveillance to provide valuable data from real world exposure. This evidence will support regulatory submissions and aid market expansion.

6. Conclusion

By amalgamating the ancient knowledge and nanotechnology, harmonizing its regulatory procedures with the global regulations, encouraging industries to run research programs on developing targeted phyto-medicine by providing financial aid and leveraging economical production, India can become a global leader in phtopharmaceutical sector. Indian pharmaceutical companies can take advantage of the rapidly growing market by providing affordable, safe and effective phytopharmaceutical formulations of International standards. With strategic planning and encouraging policies, India can explore its abundant natural resources and traditional knowledge to establish a globally competent phytopharmaceutical sector.

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Phytopharmaceutical millets: nutraceutical potential and health benefits of bioactive compounds


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Abstract

Millets, small-seeded cereal grains, are being recognized as sources of phytopharmaceuticals, bioactive compounds derived from plants with significant therapeutic benefits. These phytochemicals, including polyphenols, flavonoids, phenolic acids, saponins, tannins, terpenes, alkaloids, sterols, and glycosides, contribute to the unique health-promoting profile of millets. These compounds address chronic health concerns like diabetes, cardiovascular disorders, and cancer. Millet-derived phytopharmaceuticals, such as polyphenols, reduce oxidative stress, while saponins and sterols manage cholesterol levels, supporting cardiovascular health. With the global demand for natural and functional foods increasing, millets are emerging as sustainable, plant-based solutions to lifestyle diseases. This aligns with regulatory shifts in India, where phytopharmaceuticals are being recognized as equivalent to synthetic drugs. Incorporating millets into daily diets can provide a natural, cost-effective approach to disease prevention and management, contributing to personal and public health.

Keywords: Millets, Phytopharmaceuticals, Functional foods, Disease prevention

1. Introduction

Phytopharmaceuticals, derived from plants, are bioactive compounds that possess medicinal properties and offer significant therapeutic benefits. They have gained increasing attention due to their ability to act as natural remedies for a wide range of diseases, with minimal side effects compared to conventional pharmaceuticals. Millets, a group of small-seeded grasses, have been cultivated for thousands of years and are widely consumed in many regions, particularly in Africa and Asia (India). Indian farmer grows several species (Figure 1) such as pearl millet (*Pennisetum glaucum*), finger millet (*Eleusine coracana)*, foxtail millet (*Setaria italica*), and sorghum (*Sorghum bicolor*) (1). These ancient grains have recently gained attention not only for their resilience in harsh environmental conditions but also for their significant phytochemical value in public health. Theses mall-seeded grains are rich in a variety of phytochemicals such as Phenolic acids, Flavonoids, Tannins, Phytosterols, and Saponins. These compounds contribute to the health-promoting properties of millets.These bioactive compounds exhibit antioxidant, anti-inflammatory, anti-diabetic, and cardioprotective properties, making millets a potential dietary intervention for lifestyle-related diseases (1,2). As consumers and researchers alike focus on the role of diet in promoting health and preventing chronic diseases, millets have emerged as an important food crop due to their rich composition of bioactive compounds and essential nutrients (3).

Millets are an excellent source of nourishment. Millets are becoming increasingly popular both in India and around the world because of their potential to provide food security, environmental sustainability, and nutritional value. As part of wider measures to address global issues including malnutrition, climate change, and sustainable agriculture, both Indian and international programs are attempting to increase the production, consumption, and knowledge of millets. In order to promote the production and consumption of millets and to increase awareness of their significance as a food crop, the Food and Agricultural Organisation of the United Nations (FAO) launched the IYOM 2023 worldwide campaign. Millet awareness and consumption have increased in recent years as individuals have begun to pursue a healthier lifestyle. In 2018, India suggested 2023 as the International Year of Millets. The UN Food and Agriculture Organisation accepted it, and the United Nations General Assembly declared 2023 to be the 'International Year of Millets'. This was approved by a United Nations resolution (4).

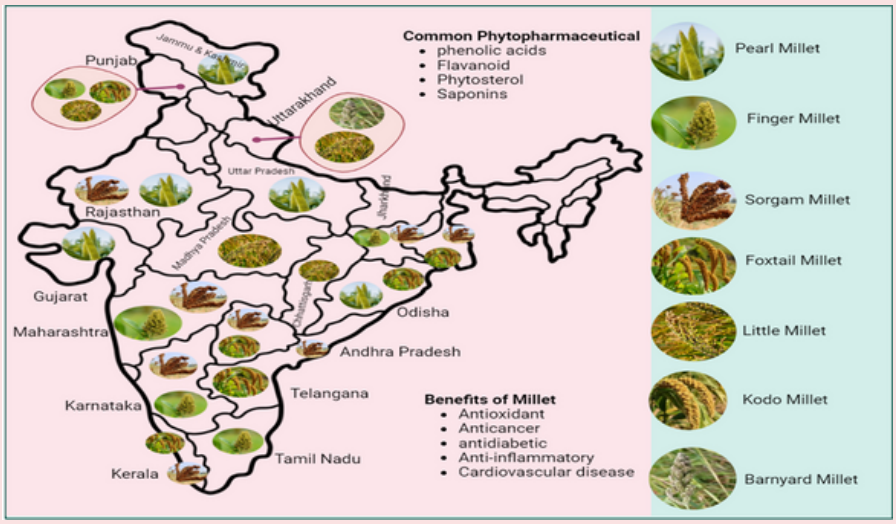


Figure 1. Geographical distribution of different species of millets in India.

The aim of this review is to explore the phytopharmaceutical potential of millets by focusing on their bioactive compounds and health benefits. Given the increasing prevalence of lifestyle diseases such as diabetes and cardiovascular disorders, understanding how millet-derived phytopharmaceuticals can mitigate these conditions is of growing importance (4).

2. Phytopharmaceuticals in millets

2.1. Polyphenols

Polyphenols are intermediates in metabolic pathways that function as defense and signaling molecules, contributing to essential biological processes. In millets, phenolic acids and, flavonoids are the primary polyphenol groups. These compounds contribute to the significant antioxidant properties of millets in both dietary and biological contexts. The seed coat of millets is especially rich in dietary fiber and polyphenols. Research suggests that millet consumption may reduce free radical induced stress in the hippocampus and downregulate genes such as γ-secretase, tau, and amyloid precursor protein, which are associated with Alzheimer's disease. Millet-derived polyphenols also show anti-diabetic properties, displaying specific hypoglycemic effects. Furthermore, bound polyphenols from millet bran, including p-Coumaric acid (p-CA) and Ferulic acid (FA), demonstrate anticancer activity. These compounds enhance the sensitivity of drug-resistant colorectal cancer (CRC) cell lines to oxaliplatin (OXA), a chemotherapy drug for CRC. Additionally, foxtail millet polyphenols induce apoptosis, inhibiting colorectal cancer progression in mice. Millet-bound polyphenols also exhibit immunomodulatory and antifungal properties (11).

Table 1. Phytopharmaceuticals in Indian grown millets

Millets	Phytopharmaceuticals	Nutritional Aspect	Ref
Sorghum bicolour L. (Sorghum)	Salicylic, protocatechuic, caffeic, sinapic, ferulic acids, p-coumaric acid), phenolic acids (gentisic, cinnamic; flavonoes (luteolin, tricin, and apigenin); flavonones (eriodictyol and naringenin)	Anti-oxidant Capacity	(5)
		Fat, carbohydrate, protein, calcium and iron	
		Essential Amino Acids	
Eleusine coracana L. (Finger Millet)	Phenolic acids (gallic, vanillic, querticin, caffeic, FA, p-CA): flavonoids (Catechin equivalent)	Protein Content, phenolic content copper, iron, manganese, zinc	(6)
		Iron, zinc, calcium, essential amino acids	
		Vitamin C	
Pennisetum glaucum L. (Pearl Millet)	3- Deoxynthocyanidin; Phenolic acids (gallic, vanillic, Chlorogenic acid, Sinapic acid, Ferulic acids, p- coumaric acid)	Phenol, soluble protein, amylase glucose, calcium, zinc, iron	(7)
		Lysine, Methionine	
		Protein and Starch Digestibility	
Setaria italica L. (Foxtail Millet)	Phenols (apigenin, N'- Caffeoyl-N'-Feruloylspermidine, Di-p-coumaroyl Spermidine, N,N',N''- diferuloyl spermidine- Dihexoside); Carotenoids (xanthophyll, Zeaxanthin)	Protein, Copper, Iron, Manganese	(8)
		Phenolic Acids, Flavonoids	
Paspalum scorbiculatum L. (Kodo Millet)	Phenolic acids (Stigmasterol, Campesterol, N-(5- hydroxy-pentyl) arachidonoylamide, Pregnenolone)	Protein, amino acids availability and starch digestibility	(9)
		Anti-oxidants, proteins, fats, carbohydrates	
Panicum sumatrense Roth. (Little Millet)	Flavonoids (6-C- Glucosyl-8-C-arabinosyl apigenin); Phenol (Sinapic acid, p-coumarylpentose, synapaldehyde, kaempferol)	Copper, iron, protein content, manganese, zinc, phenolic content	(10)
		Starch digestibility and protein	
		Flavonoids, and Phenolic Acids	

Sorghum

Finger Millet

Pearl Millet

Foxtail Millet

Kodo Millet

Little Millet

Figure 2. Assorted millets verities available in India (Source: Google images accessed on 11.11.2024)

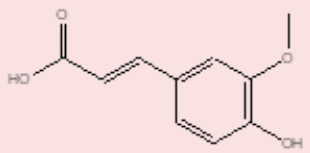
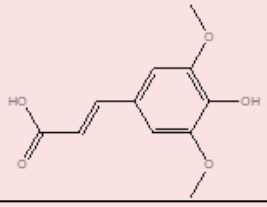
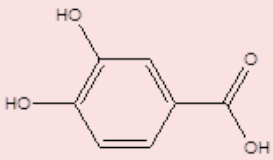
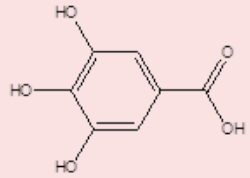
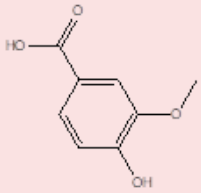
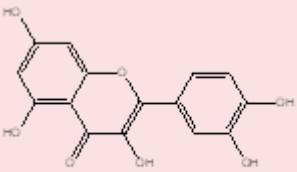
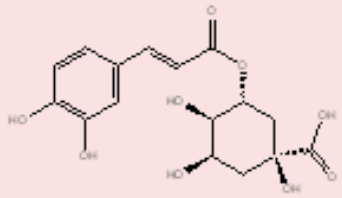
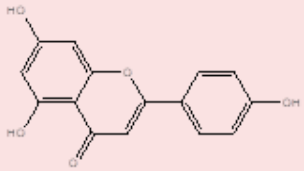
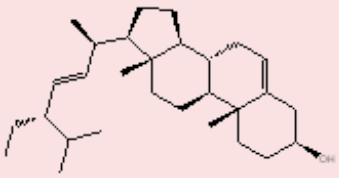
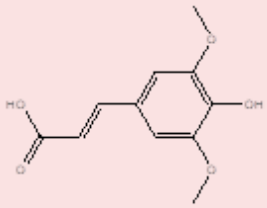
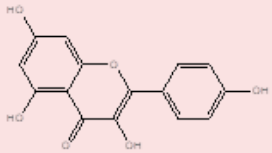
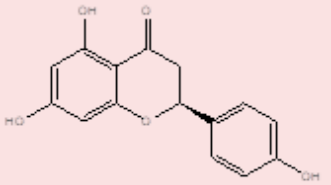
2.2.Phenolic acids

Millets, phytochemicals, and their Phenolic acids in millets originate from hydroxybenzoic acid and hydroxycinnamic acid, with content varying by millet species. The primary bound phenolic acids are derivatives of cinnamic acid, such as coumaric and caffeic acids, while free, unbound forms are typically derivatives of gallic acid, including syringic and vanillic acids. Notably, bound phenolic acids possess significant antioxidant and therapeutic properties, which are beneficial in promoting gut microbiota health and supporting overall gut function (12).

2.3 Flavonoids

Flavonoids are the primary class of polyphenols in millets, contributing valuable preservation qualities that support a balanced diet. Millet flavonoids are potent antioxidants, surpassing elements like zinc, selenium, and certain vitamins in antioxidant strength. Bhat et al. (2021) reported that millet flavonoids exhibit numerous health benefits, including anticancer, diuretic, antihypertensive, analgesic, hypolipidemic, and anti-inflammatory effects. Their Antihypertensive and Antiarrhythmic effects include the relaxation of smooth muscle in the heart, alongside LDL cholesterol oxidation prevention. Flavonoids also contribute to cholesterol reduction and inhibit platelet aggregation, while modulating the body's response to pathogens and helping to control allergens (13).

Table 2. Chemical structures of some of the phytoconstituents present in millets

		
Ferulic acid	Sinapic acid	Protocatechuic acid
		
Gallic acid	Vanillic acid	Quercetin
		
Chlorogenic acid	Apigenin	Stigmasterol
		
Sinapic acid	Kaempferol	Naringenin

2.4. Alkaloids

Alkaloids, found in millets, enhance plant condition and provide health benefits. However, alkaloids can also have genotoxic, mutagenic, carcinogenic, fetotoxic, and teratogenic effects. In foxtail millet, alkaloids have demonstrated anti-hyperglycemic and hypolipidemic effects in diabetic rat models. (14).

2.5. Terpenes

Phytosterols are produced through biosynthetic pathways, with isopentenyl pyrophosphate as a key building block for terpenoids. Terpenes, the chemical compounds responsible for the distinct aroma and flavor of millets, are primarily found in essential oils and enhance the nutraceutical qualities of the plant. These include linalool, geraniol, myrcene, and limonene. Terpenes contribute to both the sensory characteristics and health benefits of millets. Traditionally, terpenes have been valued for their roles in medicinal systems, with further potential as antineoplastic, antibacterial, and pharmacognostic agents (14).

2.6.Saponins

Saponins are known for their ability to create a soapy lather when mixed with water and have been linked to reductions in blood cholesterol levels upon ingestion. In millets, this phytochemical is primarily found in the seed coat or outer grain layers. Finger and pearl millets are particularly rich in saponins, with pearl millet having the highest content. Compared to

cereals and grasses, millets generally contain more saponins. Saponins exhibit valuable physicochemical and biological properties, making them beneficial in the food industry as emulsifying agents that improve bread porosity and aerate culinary items. Medicinally, saponins offer a variety of benefits, including anti-inflammatory, anticancer, antioxidant, and cholesterol-lowering effects (15).

2.7. Tannins

Millets comprise up to 0.61% of polyphenolic chemical substances called tannins. Millets' antioxidant capabilities, which lower aging and improve metabolic processes, are attributed to their tannins. Cultivars of millet with increased tannin content have better antioxidant qualities. It appears that different millet species have differing contents. Processing millets to increase their bio-accessibility and reduce their tannin content can lessen their anti-nutritional properties (16).

2.8. Sterols

Millet sterols, present as naturally occurring phytosterols, are secondary metabolites and essential components of plant cell membranes. Some commonly found sterols in millets include Episterol, 24-Methyllathosterol, Brassicasterol, Avenasterol, 24-Ethyllathosterol, 24-Methylenecholesterol, Isofucosterol, Fucosterol, 24-Methyl-5α-Cholest-24-en-3β-ol, and 24-Ethyldesmosterol. These sterols are typically found in millet seeds and are known for their cardiovascular benefits due to their structural similarity to cholesterol. By competing with cholesterol for absorption in the intestines, millet sterols effectively reduce cholesterol levels in circulation. As a result, regular millet consumption supports a balanced diet, promoting overall health and well-being. Fortifying millet products by increasing sterol content can enhance their nutritional value (17).

2.9. Glycosides

Glycosides in millets are compounds formed by sugar molecules linked to other functional groups. Key glycosides, include Kaempferol glucoside, Catechin/epicatechin glucoside, and Glucosyl orientin. Millets also contain esterified sterol glycosides and sterol glycosides, which are classified as millet glycolipids. These glycosides, as phenolic compounds in millet grains, contribute to reducing the risk of chronic diseases and enhance the antioxidant and anti-inflammatory properties of millets. Additionally, millet malts contain higher levels of free sugars and non-starchy water-soluble polysaccharides compared to unprocessed millets (18).

3. Conclusion

Millets have significant phytopharmaceutical potential, promoting health and preventing diseases. Their diverse phytopharmaceuticals, including polyphenols, flavonoids, alkaloids, terpenes, saponins, tannins, sterols, and glycosides, offer a sustainable and accessible solution to chronic health issues. As research continues, millets can be incorporated into functional foods and nutraceuticals, promoting healthier dietary choices and effective health management. This holistic approach to healthcare aligns with the growing preference for natural, sustainable solutions in modern society.

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Utilizing phytopharmaceuticals to rejuvenate the immune system: An exciting prospect in India



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Abstract

This review's objective was to compile the significant Phytopharmaceuticals with strong immunomodulatory properties that are confined to consuming in our daily life. The word "Phytopharmaceutical" is derived from the Greek roots "Phyton" (plant) and “Pharmakon” (medicine). It also discussed the function of natural products in the boosting up of immune system to combat many diseases and disorders. For a variety of chronic conditions, including cardiovascular, renal, and autoimmune diseases, these phytomedicines made from the roots, stem, tuber, flower, seed, and leaves were found to possess medicinal properties. In this significant harmony, a compromise or overreaction might have devastating consequences, including autoimmune, immunodeficiency-related, or inflammatory disorders. Conversely, immunological competency may be significantly influenced by nutrition. As prevention is better than cure, it is always acceptable to include such medicinal plants which are easy to ingest and get benefit in terms of being healthier and devoid of ailments.

Keywords: Phytopharmaceuticals, immune system, Indian system of Medicine, Spices

1. Introduction

Phytopharmaceuticals derived from the natural sources are used for diagnosis, prevention and treatment of diseases in animals and humans, both externally and internally but not for parenteral use as per Drugs and Cosmetics Act, 1945, as specified in Rule 2 (1). Phytopharmaceuticals are derivatives of plants with immense pharmacological potential. From decades, plants have been crucial in the Indian ancient medicinal system. These are easily accessible and also have no side effects. As the adverse drug reactions stands as a major concern for public health, can be avoided by substituting synthetic drugs with plant-based medicines (2). This writeup mainly focused on such type of phytopharmaceuticals which are included as food in our daily life. This is because of easy consumption and human compliance.

2. Noteworthiness of immune system

Immune system protects the body from various pathogens such as bacteria’s, viruses and fungi. Once our body get expose to any microorganism or antigen, body’s immune system gets activated and prevent our body from antigens by eliminating from the body (Figure 1). On the contrary, overactive immune system can cause development of auto-immune disorders such as psoriasis, myasthenia gravis and so on. For achieving a good immunity, it is necessary to take adequate number of vitamins and minerals. Phytopharmaceuticals and its constituents can play a role in providing adequate nutrition to a person.

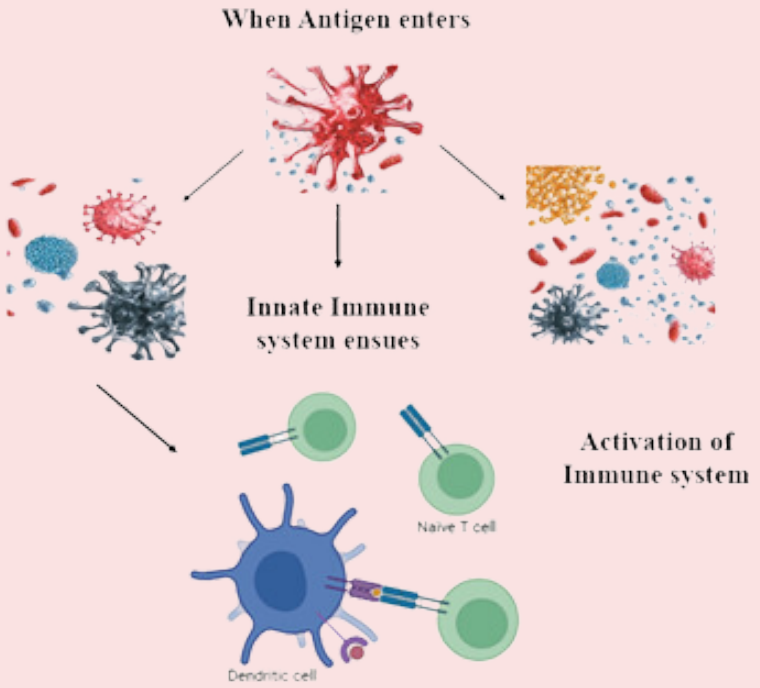

Figure 1. Activation of Immune system with an entry of antigen

3. Phytoactive constituents as immune system boosters

These are essential components of Phytopharmaceuticals, which are extracted from medicinal plants. Phyto active compounds can be flavonoids, terpenoids, carotenoids and polyphenols etc. These compounds have antioxidant properties which can be useful for treating plethora of immune diseases by boosting up the immunity. It is an ideal way to consume herbs, spices and vegetables as a part of our daily diet to improve immunity and prevent from immunodeficiency disorders (3). Phyto active compounds of various Indian medicinal plants are listed in Table 1.

Table 1. Various Indian medicinal herbs and spices with their phytoactive constituents

Common name	Scientific name	Phyto active constituents	Ref
Turmeric	*Curcuma longa*	Curcumin	4
Cinnamon	*Cinnamomum zeylanicum*	Cinnamaldehyde and trans-cinnamaldehyde (Cin)	5
Ginger	*Zingiber officinale*	Gingerols, shogaol, & paradols	6
Garlic	*Allium sativum*	D-Linalool, Methyl chavicol, eugenol cineole, Allyl sulfides, allicin, ajoene, S-allyl-L-cysteine (SAC)	7
Black pepper	Piper nigrum L	β-pinene, piperine, oleoresins, piperolein, limonene, lignans, alkaloids, flavonoids, myristic acid, myristicin, citral, palmitic acid, piperine, and lauric acid	7

Fenugreek	Trigonella foemum graecum	Pigenin, kaempferol, quercetin, vitexin, tricin, saponins, naringenin, Sesquiterpenes, aromatic aldehydes, terpenes,	7
Cloves	*Syzygium aromaticum*	Eugenol, caryophyllene, dehydroeugenol sesquiterpenes, tannins, isoeugenol acetyleugenol pinene, vanillin, flavonoids, phenolic acids, gallic acid	7
Tulsi	*Ocimum basilicum L*	Catechins, quercetin, rutin, kaempferol, anthocyanins, limonene, terpinene, carvacrol, geraniol, menthol, safrole, tannins, ursolic, p-coumaric, and rosmarinic acids and D-linalool, methyl chavicol, eugenol cineole, and apigenin	7
Amla	*Emblica officinalis*	Tannins, flavonoids, polyphenols, amino acids, fixed oils and vitamins	8
Neem	*Azadirachta indica*	Flavonoids, polyphenolic compounds, Quercetin, nimbin, nimbidin nimbolide,ascorbic acid	9
Drum stick	*Moringa oleifera*	Carotenoids, glucosinolates, flavonoids, tocopherols, and phenolic acids polyunsaturated fatty acids and folate	10
Black seeds	*Nigella sativa*	Coumarins, γ-terpinene, safranal, quercetin, p-coumaric, rosmarinic, trans-2, dihydrocinnamic acids flavonoids	7
Oregano	*Origamum vulgare L*	Thymol, carvacrol, α- β-caryophyllene, carnosic acid, carnosol, caffeic acid, rosmarinic acid, flavonoids	7

Various Phytopharmaceuticals (structures shown in Figure 2) which are commonly found in Indian herbs, spices and daily vegetables are as follows (11):

3.1. Resveratrol: It is considerably found in grapes, peanuts, mulberries, peanuts, blueberries, strawberries. They have antioxidant, anti-aging and anti-carcinogenic properties.

3.2. Probiotics and prebiotics: Probiotics are found in fermented foods and also be taken through supplements. Prebiotics are found in soybeans, greens, banana, garlic onions etc.

3.3. Phytosterols: It is generally found in vegetable oils, fruits, nuts and legumes. They have significant effect on lowering LDL.

3.4. Isoflavonoids: These are present in soybeans, soy cheese, and tofu. They prevent osteoporosis and cancer.

3.5. Flavonoids: Generally found in berries, legumes, tea, grapes, cocoa, spices, fruits, green vegetables, onion, apple, olive oil, walnuts and peanuts. They have antioxidant, antimicrobial and anti-inflammatory properties.

3.6. Carotenoids: They are carotenoids are α-carotene, β-carotene, zeaxanthin, lutein, and lycopene. They are present in color foods carrot, tomato, lettuce, broccoli, squash, red pepper etc. They have anti-oxidant property and protects against various cancers.

3.7. Omega-3 fatty acids: Fishes are main source of omega-3 fatty acids, specially, salmon, mackerel, herring, rainbow trout, and sardines.18-carbon omega-3 fatty acid, alpha linolenic acid are found in soybean, canola and flax seed oil.

3.8. Lycopene: specifically present in tomatoes and prevent against cardiovascular diseases and cancers.

3.9. Anthocyanins: Red cabbage, cherry, blueberry, and cranberry. They help in preventing hyperlipidemia and diabetes.

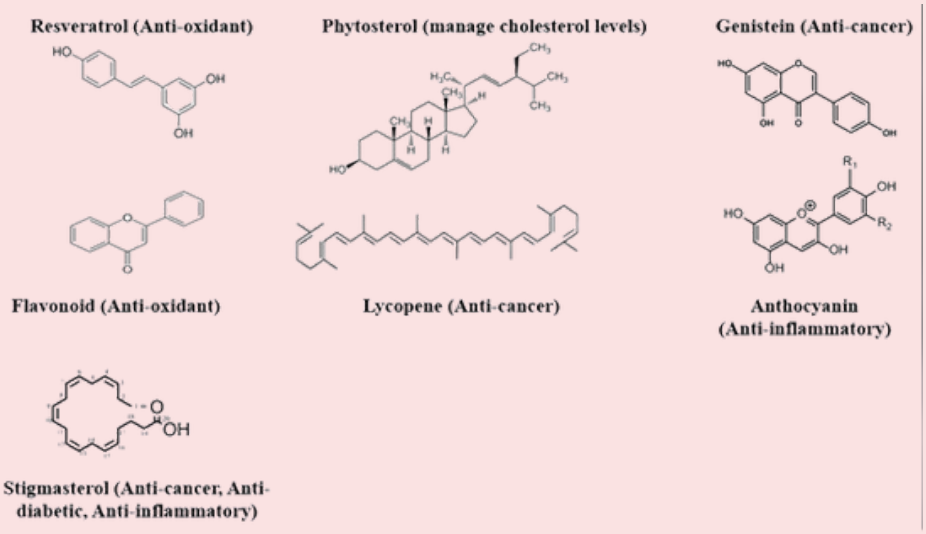

Figure 2. Chemical structures of phytochemical constituents with their activities

4. The rationale behind selecting phytopharmaceuticals to strengthen the immune system

Antioxidant potential of these Phytopharmaceuticals help in reducing oxidative stress which directly improves immunity. Human body undergo oxidative stress and cell damage due to psychological stress, environmental pollutants, polluted food, alcoholism and smoking. Thus, Indian diet food with all spices and herbs on daily basis can have an ameliorative effect in various ailments/health conditions (12). Contemporary sedentary lifestyle is making people deficient of nutrition and intake of junk food also contribute to declined immunity hence giving less priority to healthy easily accessible food at home.

To optimize the nutrition and promote a healthy immune system, the World Health Organization (WHO) advises people to eat a range of fresh, unprocessed meals every day. In order to reduce the risk of health issues and chronic diseases, they also advise avoiding excessive amounts of added sugar, fat, and sodium. Numerous health and wellness advantages are readily achievable by heeding their advice (13).

Additionally, the Food and Drug Administration (FDA) recognized all spices and herbs as safe for human consumption. Generally, herbs and spices are low in calories, fats and salt, thus, adding them into our daily diet will support immunity (14). Many plant-based drugs prevent cell damage due to their anti-oxidant and anti-inflammatory property. COVID-19 era was an excellent example, when significant improvement in immunity was seen on dietary interventions with Indian herbs and spices (15,16).

5. Mechanism of action of phytopharmaceuticals in activation of immune system

Phytopharmaceuticals act in different mechanisms to modulate immunity like Phagocytosis, activation of macrophage, cytokine secretion, antibody production, proliferation of lymphocytes as depicted in Figure 1.

It is well known that plant-based nutritional diets increase the number of good bacteria in the intestines, which support and make up as much as 85% of the immune system. The immune stimulation capacity of spices and their secondary metabolites was also demonstrated. The big intestine lining is known to benefit from non-digestible nutrients that specifically encourage the growth of proper intestinal bacterial flora. These nutrients may either attach to epithelia or be absorbed in the systemic circulation to boost the immune system after being digested by gut bacteria. Immunomodulation factors that have been examined include interferon-alpha (rINF-α), recombinant interferon-gamma (rINF-γ), and so on, possessed a strong antiviral activity and were suggested for usage either therapeutically or prophylactically in early-stage infections of several virus species.

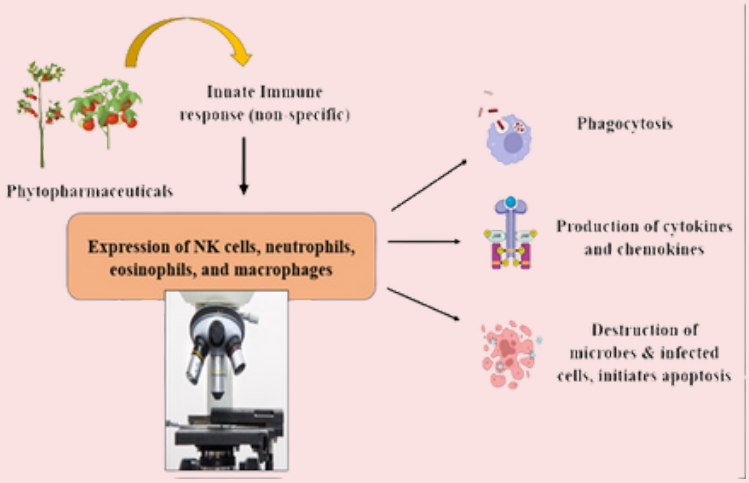

Figure 3. Mechanism of action of phytopharmaceuticals in activation of immune system

6. Conclusion

This article highlighted the significance of daily consumption of Indian herbs and spices that were considered as phytopharmaceuticals as a part of our daily diet. We Indians are fortunate to possess herbs like turmeric, fenugreek and curry leaves with immense medicinal properties that are consumed daily in our life, without which it is absolutely not possible to complete a meal. These herbs and spices consist of excellent therapeutic Phyto active constituents, which can be helpful for enhancing immunity and protection against infections. A human always relies on such type of phytopharmaceuticals that are beneficial all the time and doesn't need to include them as a separate medication.

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Berberine: Leveraging a potent phytochemical for advancing India's therapeutic innovations


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Abstract

Berberine, a quaternary isoquinoline alkaloid derived from plant *Coptis chinensis*, exhibits a broad spectrum of pharmacological properties that position it as a promising candidate for treating numerous health conditions, including cancer, digestive disorders, metabolic syndromes, cardiovascular diseases, and neurological ailments. In digestive health, berberine enhances the intestinal epithelial barrier, inhibits pathogenic bacteria such as *Helicobacter pylori*, and mitigates liver injury. Its anticancer effects are compelling, as it inhibits cell proliferation and metastasis. Additionally, berberine regulates glycometabolism and lipid metabolism, promoting weight loss. Cardiovascular benefits include improved hemodynamic function, reduced hypertension, and prevention of atherosclerosis, supported by its ability to enhance endothelial function. Furthermore, its neuroprotective effects, characterized by antioxidative, antiapoptotic, and anti-ischemic properties. Overall, while extensive research has explored berberine's mechanisms and therapeutic applications, much remains to be understood, emphasizing its potential as a versatile therapeutic agent for managing chronic cardiometabolic disorders.

Keywords: Berberine, cardiovascular, anti-cancer, *Coptis chinensis,* anti-inflammatory, Antibacterial

1. Introduction

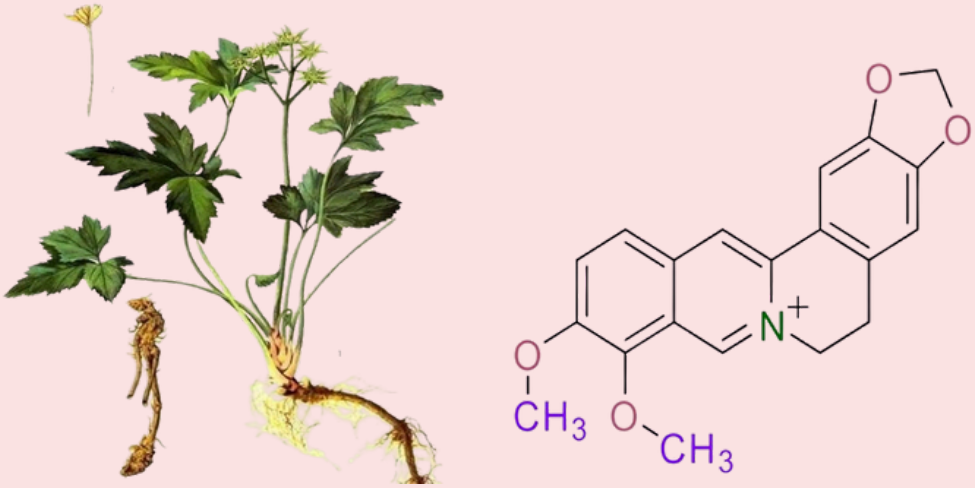
For the treatment of chronic illnesses, the use of natural, traditional remedies is being promoted because synthetic medications may have unanticipated side effects. A traditional plant alkaloid with antibacterial and antiprotozoal qualities, berberine is employed in Chinese and Ayurvedic medicine. It's interesting to note that recent clinical studies on berberine have uncovered its diverse pharmacological characteristics and multi-spectrum medicinal uses (1).

Berberine can treat various illnesses, including cancer and digestive, metabolic, cardiovascular, and neurological disorders. It inhibits microbes, lessens liver damage, and guards against gastrointestinal issues. Additionally, berberine inhibits the development of cancer cells, inhibits invasion and metastasis, and possesses neuroprotective qualities (2).

2. Botany and phytochemistry

Berberine is a natural alkaloid found in various plants, primarily in the roots, bark, and stems. Indigenous sources include *Berberis aristata* (Indian Barberry), *Berberis vulgaris* (European Barberry), *Berberis aquifolium* (Oregon Grape), and *Coptis chinensis* (Chinese Goldthread), commonly used in traditional medicines across Asia and Europe. Non-indigenous sources are *Berberis thunbergii*

(Japanese Barberry) and *Hydrastis canadensis* (Goldenseal), which are prominent in North America. Other sources include *Phellodendron amurense* (Amur Cork Tree) from East Asia and *Tinospora cordifolia* (Giloy) from India. The roots and rhizomes are typically the richest in berberine, followed by bark and stems (1,2). The perennial herb *Coptis chinensis* has rhizomes that are yellow and branching. The leaves have three lobes and are somewhat leathery. The fruit is typically harvested between April and June, with flowering taking place between February and March.This plant grows between 500 and 2000 meters above sea level in valleys or mountain woods (3).



(a) (b)

Figure 1. a) Image of *Coptis chinensis*; b) chemical structure of Berberine

Berberine is a yellow solid with a melting point between 145.1 and 146.7°C. It dissolves in hot water but only slightly in cold water or ethanol, and is insoluble in organic solvents like ether and benzene. Its structure features a dihydroisoquinoline ring and an isoquinoline ring, consisting of four rings labeled A, B, C, and D. The methylenedioxy group formed by the C2 and C3 of the A ring is crucial for its biological activities, including anticancer effects. The quaternary ammonium structure in the C ring contributes to its antibacterial properties, while hypoglycemic action arises from modifications in the D ring through acylation or alkylation. Notably, C8 and C13 alkylation enhance its cytotoxicity (4).

3. Berberine isolation

Berberine is an isoquinoline alkaloid that is usually extracted by isolating it from a variety of plant sources, such as *Phellodendron amurense*, *Coptis chinensis*, and *Berberis species*. One of the study described in detail how ethanol can be used as a solvent for effective extraction, highlighting its benefits in terms of purity and yield. In order to separate the alkaloid, the procedure usually comprises macerating the plant material, adding the solvent, and then filtering the mixture (5).

Techniques including microwave-assisted extraction and ultrasonic-assisted extraction, which increase extraction efficiency and cut down on time, have been investigated for further improvement of the extraction process (6). These contemporary methods can minimize the degradation of sensitive chemicals while greatly increasing the output of berberine.

Coptis chinensis (Chinese Goldthread) yields more berberine than other plants due to its high alkaloid concentration in the rhizomes, which can reach over 5-10% of the dry weight. The plant's native environment cool, moist, and shaded forests in East Asia supports optimal berberine synthesis, while its genetic makeup enables efficient alkaloid production. Traditional cultivation methods also allow for extended growth periods, further increasing berberine levels (7).

4. Pharmacological effect

For cancer, inhibiting cancer cell growth, decreasing metastasis, inducing apoptosis, activating autophagy, controlling gut microbiota, and enhancing the effects of other cancer therapies are the key anticancer actions of berberine. Nevertheless, its low water solubility and poor oral bioavailability may lessen its antitumor properties (8).

As an anti-hyperglycemic agent, berberine influences glucose metabolism by promoting glycolysis through elevated glucokinase activity, boosting insulin secretion, and inhibiting hepatic adipogenesis and gluconeogenesis, all of which are mediated by AMP- activated protein kinase (AMPK) activation (9). In addition to its anti-diabetic properties, berberine has been shown to have antioxidant properties via lowering the buildup of reactive oxygen species and to have anti-inflammatory properties (8).

Additionally, early clinical data points to berberine's potential to improve vascular health by lowering endothelial inflammation, even in individuals with pre-existing cardiovascular conditions. The evidence that is now available points to the potential utility of berberine in the treatment of long-term cardiometabolic diseases (10).

5. Clinical potential

The importance of berberine in modern antimicrobial stewardship was emphasized by a meta- analysis that focused on its usage in treating illnesses brought on by strains of bacteria that are resistant to drugs (11). A crucial area of research has also been the compound's capacity to alter the composition of the gut microbiota, suggesting that berberine may improve gut health and reduces systemic inflammation (12).

6. Epidemiology

The increasing importance of berberine in treating illnesses like viral infections and metabolic disorders is demonstrated by epidemiological research conducted in India. Given that about 30% of urban individuals have metabolic syndrome symptoms, berberine is a promising treatment option since it may enhance insulin sensitivity and lipid metabolism (9).

Furthermore, given the rise in antibiotic resistance, berberine's antibacterial qualities are becoming more and more significant. Research suggests that berberine is a possible alternative treatment since it effectively combats prevalent infections in Indian healthcare settings (13). The incorporation of berberine into both contemporary and conventional Ayurvedic methods highlights the plant's growing significance in Indian health and the need for more epidemiological studies to evaluate its effects on public health.

7. Pharmacovigilance

Berberine pharmacovigilance research has become crucial for determining the drug's safety and effectiveness in clinical settings. Despite the lengthy history of berberine's usage in traditional medicine, new systematic studies have brought attention to the need for thorough monitoring of any negative effects. The most frequent adverse effects of berberine, according are gastrointestinal disorders such diarrhea and constipation (14).

Regarding safety, berberine may interact with a number of drugs, especially those that are broken down by cytochrome P450 enzymes. For example, because of possible changes in drug metabolism, its concomitant use with anticoagulants or antihypertensive drugs may need close monitoring (15).

8. Cultural and economic impact

As a natural cure with profound cultural roots in traditional Indian medicine, especially Ayurveda, berberine is highly valued. Its relevance in holistic healthcare methods is highlighted by its historical use to treat a variety of illnesses, such as metabolic and gastrointestinal diseases. Its use into herbal formulations and nutritional supplements reflects the cultural acceptability of berberine as a medicinal agent, encouraging a fusion of traditional knowledge and contemporary health trends. This acceptability is demonstrated by consumers' increasing interest in natural alternatives for the treatment of chronic illnesses, which is consistent with the global trend toward herbal therapy (16).

In terms of the economy, the demand for berberine has helped the Indian herbal supplement market expand. Local farmers and manufacturers are profiting from the production and extraction of berberine-rich plants, like Berberis species, as consumers look for natural products more and more. This change encourages sustainable farming methods in addition to helping local businesses. According to the study, the market for herbal supplements, such as berberine, is expected to expand

dramatically, improving incomes and generating employment possibilities in rural regions. Additionally, as berberine becomes more popular in both local and foreign markets, more money may be spent on research and development, opening the door for creative uses in the medical field (17,18).

9. Conclusion

Berberine stands out as a potent phytochemical with multifaceted therapeutic potential, particularly within the Indian healthcare context. Its historical roots in traditional medicine, coupled with emerging scientific evidence, position berberine as a promising agent for managing a range of chronic conditions, including metabolic disorders, cancer, cardiovascular diseases, and infections. The pharmacological actions of berberine, such as enhancing insulin sensitivity, reducing inflammation, and exerting antimicrobial effects, underscore its versatility and applicability in modern medicine.

The cultural acceptance of berberine as a natural remedy aligns with a broader global trend toward herbal therapies, driving both consumer interest and economic growth in the herbal supplement market. As India grapples with increasing rates of lifestyle-related diseases and antibiotic resistance, berberine offers a sustainable and effective solution that bridges the gap between traditional and contemporary healthcare practices.

However, to fully realize berberine's clinical benefits, ongoing research is essential. Pharmacovigilance studies must continue to ensure its safety and efficacy in diverse populations, while further exploration of its mechanisms and applications can unlock new therapeutic avenues. As such, berberine not only represents a valuable addition to the therapeutic arsenal but also exemplifies the integration of ancient wisdom with modern scientific inquiry, paving the way for innovative health solutions in India and beyond.

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Crocus sativus: The future of anti-cancer medicine in India

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Abstract

As we all know, India is rich in its biodiversity as well as it has an ancient tradition of Ayurveda. Phytopharmaceuticals are those that are derived from plants and plant-based compounds that have already been used for centuries in traditional Indian medicine. In this issue, we delve into the latest research advances in phytopharmaceuticals, industry trends, and policy initiatives shaping the future of phytopharmaceuticals in India. Nowadays cancer is one of the main threats to healthy people in all over the world. One of the most recent research and review shows the anti-cancer properties of phytoconstituents i.e. Crocin and Crocetin of plant Saffron. Saffron is widely obtained from the flower of Crocus sativus, mainly known as the plant Crocus Saffron. This vibrant orange-red spice has been cherished for centuries, not only for its unique flavour and colour but also for its medicinal properties. In India, saffron holds a special place in both culinary and traditional medicinal practices, particularly in Ayurveda.

Keywords: Phytoconstituents, volatile, biodiversity, chemoprevention, spice, apoptosis.

1. Introduction

One of the newer research projects includes the "*Crocus sativus*" species which belongs to the family 'Iridaceae'& it predominantly thrives in regions spanning from the Mediterranean Sea, through Iran, and extending to India, Tibet along some regions of China (1). In India it is used in food additives for tasting purposes, flavouring agent and colouring agent but it was found that it had some therapeutic properties.

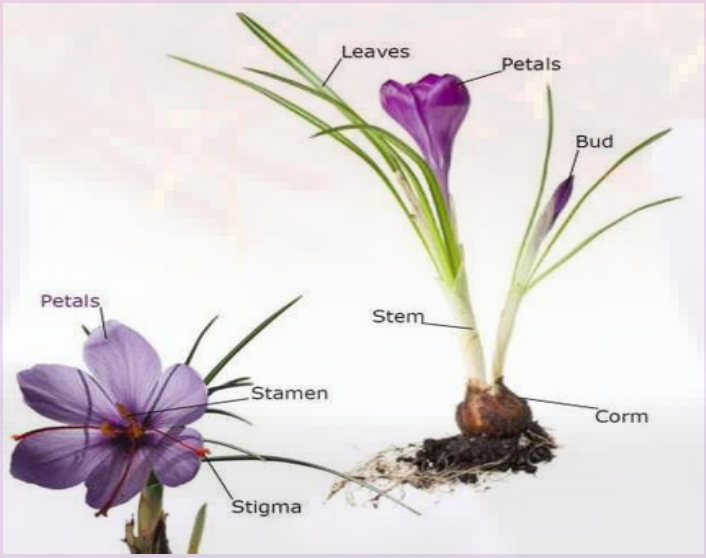

Figure 1. Different parts of plant *Crocus sativus*

The phytoconstituent “Crocin” is obtained from dried stigmas of the plant Crocus sativus (saffron) and it is regarded as one of the most potent & effective anti-cancer therapeutic components of saffron stigma. Saffron is traditionally used to treat many diseases including multiple cancer, neurological defects, cognitive, inflammatory, allergy, autoimmune, coeliac, glomerulonephritis, hepatitis, inflammatory bowel, pre-perfusion injury, and neural and cardiovascular inflammations (2). Chemoprevention is a commonly used method that prevents cancer development, along with some other newer emerging treatments like radiotherapy, photodynamic therapy, catalytic therapy, and sometimes surgery (3). A suitable strategy to prevent cancer involves a combination of methods, which includes the usage of some agents that are synthetic and natural which inhibit cancer growth. The saffron can be turned out as an anti-cancer medicine in the future.

2. Chemistry of saffron

Saffron is obtained from the dried stigmas of *Crocus sativus* and is a spice renowned for its culinary, medicinal, & cultural significance. Its chemistry and anti-cancer properties are of particular interest:

Saffron's bioactive compounds includes:

- **Crocin (8-10%):** Water-soluble carotenoid pigment, responsible for its colour and anti-cancer properties.
- **Crocetin (1-3%):** Lipophilic carotenoid, contributing to its anti-cancer and antioxidant activities.
- **Safranal (0.5-1%):** Volatile oil, possessing antioxidant and anti-inflammatory properties.
- **Picrocrocin (1-2%):** Monoterpenoid glycoside, responsible for its bitter taste (4).

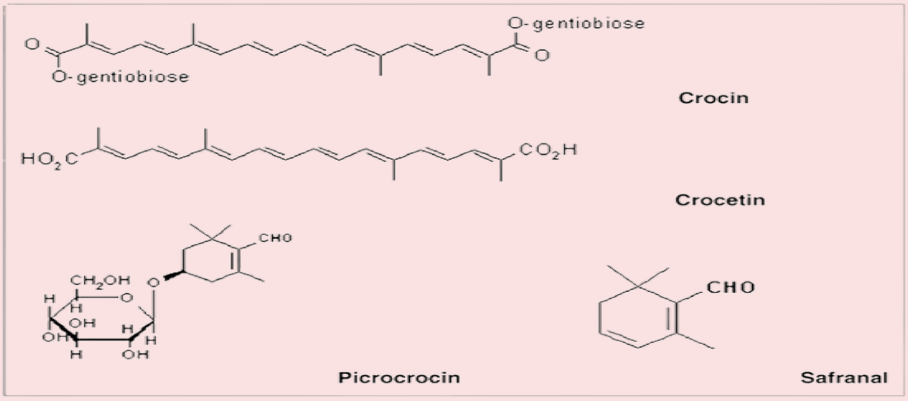

Figure 2. Different chemical constituents of plant Saffron

Saffron constitutes approximately 150 compounds, including both volatile and non-volatile, as well as certain aroma-producing substances that are lipophilic i.e lipid soluble and hydrophilic i.e water-soluble carbohydrates, and also proteins, a few minerals, some vitamins & mucilage. Based on the chemical analysis performed on the dry stigmas of saffron extracts, carotenoids, especially crocin & crocetin are the key secondary metabolites in saffron, such as the aldehydes picocrocin and safranal, play an essential role in the anticancer activity of the saffron (5).

2.1. Crocin

Crocin is a key compound in saffron (Crocus sativus), primarily responsible for its vibrant red color. Its molecular composition is $C_{44}H_{64}O_{24}$, with a molecular mass of 976.96 g/mol. Crocin exists in several forms, including Crocin 1-5, with Crocin 1 (also known as α-crocin) being the most abundant and widely studied phytoconstituent (6). The sugar groups in Crocin 1 enhance its solubility in water, which contributes to its high bioavailability and widespread use in various applications for example most importantly for anticancer activity.

2.2. Crocetin

Crocetin is a natural carotenoid with an amphiphilic structure, featuring a molecular composition of $C_{16}H_{24}O_4$ and a molecular weight of 328.4 g/mol (7). It melts at a temperature around 285°C. Crocetin is a key compound that gives saffron its unique color, comprising approximately 14% of its complete dry weight.

2.3. Picocrocin

Picocrocin, with the molecular composition $C_{16}H_{26}O_7$ and a molecular mass of 330.37 g/mol. It is the main glucoside that has a bitter taste, crystalline, and is present in saffron. It is the compound responsible for saffron's characteristic taste. In addition to imparting bitterness, picocrocin also contributes to saffron's therapeutic properties. When hydrolyzed, picocrocin breaks down into glucose, and the aldehyde compound safranal (8).

2.4. Safranal

Safranal, with the molecular formula $C_{10}H_{14}O$ and a molecular weight of 150.21 g/mol, is the primary volatile compound responsible for saffron's distinctive aroma. It is one of the key aromatic constituents of saffron, making up approximately 60% of its volatile components (9). This compound has demonstrated anti-inflammatory effects and promote apoptosis in cancerous cells.

3. Cultivation of saffron

For the cultivation of saffron, this plant need an cold and dry places. A very large number of flowers are required to produce some amount of saffron lile 6 kg saffron yeilds from 9,00,000 flowers of Crocus sativus. In India cultivation of saffron is suitable in areas of Jammu and Kashmir. Some recent research and initiatives expanded farming to regions of Himachal Pradesh and Sikkim also.

3.1. Cultivation requirements

Crop thrives in well drained loamy soil with organic contents. High altitude areas and regions having well drained soil and ambient temperature along with well suited climate condition is required for the saffron cultivation. In India, regions with high altitude are Jammu and Kashmir, Himachal Pradesh and sikkim can be a leading producer for its cultivation.

3.2. Economic potential

As the international demand of Saffron increases beacuase of both therapeutic effect and economical benefits, India can become an leading exporter for saffron. Saffron can be emerge as a valuable export crop for India, that fosters the economic growth and generating the income for local farmers in India.

3.3. Challenges in saffron cultivation

Despite having its potential, Indian saffron cultivation faces challenges including climate change,heavy rainfall, snowfall, land slides , pest and insect issues and low productivity or yield due to traditional farming methods by indian farmers.

3.4. Government initiative

The Indian Government has recognise the imporatnce of saffron cultivation in India, they started an National Saffron Mission in 2010-2011 to support the saffron cultivation in Jammu and Kashmir. It also aims to improve cultivation practice, providing financial assistance and establiush better irrigation facilities and techniques in Kashmir.

Not only in Kashmir, India has power to produce saffron in many regions like Himachal Pradesh and Sikkim, The government need to emphasize more on this as it become commercially important crop for export as well as India can become the larger producer of Saffron.

4. Anti-cancer property of saffron

Saffron, obtained from parts of the plant Crocus sativus, is not only a culinary spice but also a potent medicinal herb. Some of its active components have shown anti-cancer properties but it also shows other medicinal uses and values as represented in figure 3.

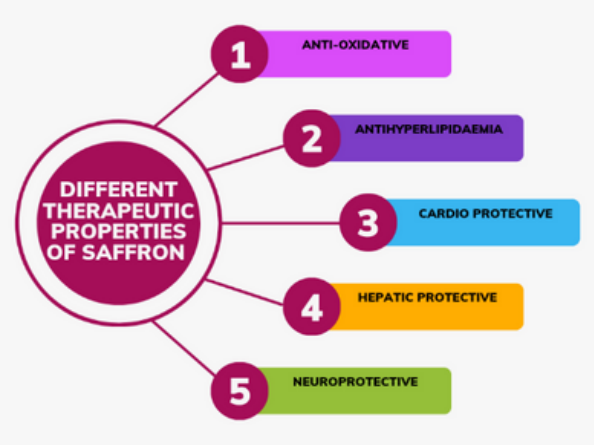

Figure 3. Different therapeutic properties of phytoconstituent of saffron

Crocin can be solubilized in water & it is a carotenoid that is commonly used orally. Among the all primary phytoconstituents found in Saffron's flowers crocin & crocetin, crocin is noted for having the most potent anticancer properties. It has been shown exhibit pro-apoptotic and antiproliferative effects (10). The property of getting solubilized in water, combined with its strong inhibitory effects on cancer cells, makes crocin a promising compound for cancer treatment and prevention (11). Saffron prevents carcinogenesis, triggers programmed cell death, prevents metastasis, and blocks angiogenesis.

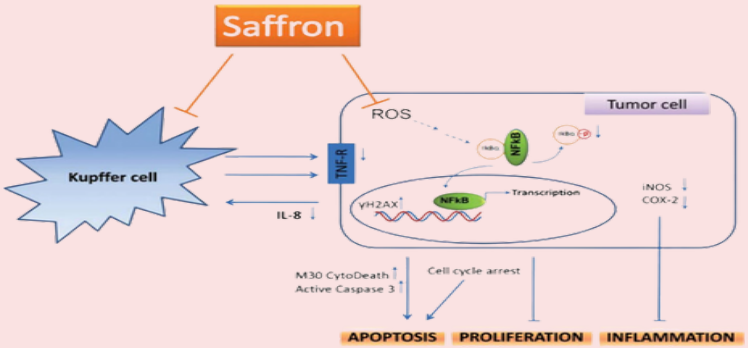

Figure 4. Mechanism of action of saffron on cancer cells

4.1. Enhanced efficacy with liposome encapsulation

Saffron's tumoricidal activity is more pronounced when administered parenterally than orally. Encapsulating saffron in liposomes has been shown to markedly reduce the growth of transplanted tumor cell in mice (12).

4.2. Effectiveness in mice

In athymic mice, crocetin has been shown antitumorigenic properties against the pancreatic cancer by inhibiting the growth of tumor cell this inhibition (13). It is found that the crocetin is safer for ATRA-sensitive cancers.

4.3. Increased survival and reduced tumor growth

Liposome encapsulation further enhances its antitumor activity, significantly inhibiting tumor growth (14).

4.4. Immunological activation

Saffron encourages nonspecific increase in lymphocyte proliferation during in vitro studies. This implies that its antitumor effects might be facilitated through immune system pathways (15).

4.5. Selective action in rats

Decreased tumor growth rate in rats with colorectal tumors, with a more pronounced effect in females (16). This indicates that hormonal factors might influence crocin's effectiveness.

4.6. Provitamin A activity

Saffron carotenoids have been suggested to possess provitamin A activity, which might contribute to their anticancer effects (17).

4.7. Induction of apoptosis

Crocin induces programmed cell death (apoptosis) in cancer cells, as evidenced by microscopy studies showing cell shrinkage and pyknotic nuclei in treated HeLa cells (18).

4.8. Selective cytotoxicity

A bioactive agent isolated from saffron corms has shown selective cytotoxicity, being significantly toxic to cancerous cells (19).

5. Conclusion

The mechanisms through which saffron exerts its anticancer effects are diverse. Additionally, saffron has shown the ability to inhibit genotoxicity and enhance the immune response, further contributing to its antitumor activity. The low toxicity of saffron, combined with its high efficacy, makes it a promising candidate for cancer chemoprevention and therapy.

Despite the promising results from animal and laboratory studies, the exact mechanisms of saffron's anticancer effects remain unclear, and its efficacy in humans has yet to be confirmed through clinical trials. Modern biotechnological methods and indoor cultivation could help produce high-quality saffron at lower cost, making it more accessible for widespread use. In conclusion, the accumulated evidence suggests that saffron holds significant potential as an anticancer agent. Future research should focus on conducting clinical trials to verify its effectiveness in humans and further investigate the underlying mechanisms of its antitumor activities. The continued exploration of natural compounds like saffron could lead to developing a new, effective cancer treatments and preventive strategies.

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Therapeutic potential of naringenin in the management of CVS and related problems: A comprehensive review

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Abstract
According to epidemiological research, Western-style food patterns are among the factors that influence the emergence of diabetes, dyslipidemia, and cardiovascular diseases. According to recent research, a high-fat diet is responsible for the development of cardiovascular risk in both humans and animals. It has been demonstrated that dietary components derived from plants, such as polyphenolic chemicals (such as flavonoids, anthocyanines, and phenolic acids), may have health benefits for the therapy of obesity, hypertension, and cardiovascular illnesses. Among these bioactive substances, flavonoids make up a significant fraction, and another of the most considerable flavonoids is naringenin. Naringenin lowers elevated plasma levels and has a vasodilation effect, making it useful in the treatment of atherosclerosis and hypertension. It is a good scavenger of free radicals and can prevent oxidative stress. The mechanisms and pharmacology of naringenin as a potential bioactive compound against cardiovascular diseases will be discussed in this article.

Keywords: Cardiovascular Diseases, Oxidative Stress, Naringenin

1. Introduction
Since the earliest time, man has used plants for a diversification of purposes, including food and medicinal. Currently available medications frequently have natural ingredients (1). More than 1/4th of all prescribed medications worldwide is procured from plants, and many of these potent phytoconstituents are used for a diversification of ailments (2). Flavonoids are crucial herbal additives with unique organic activities. A significant series of flavonoids includes citrus flavonoids. Naringenin and hesperidin, two flavonoids that are unquestionably in demand, are frequently appearing in a few safe-to-eat fruits and vegetables as aglycones and glycosides (3). Naringenin has been mentioned for hypocholesterolemic, antiestrogenic, hypolipidemic, antihypertensive and anti-inflammatory activities. It can be repose among the numerous citrus fruits, orange blossoms, tomatoes, vegetables, and herbs. The primary focus is also on an important property that would be the cardiovascular protective property of naringenin.

2. Effects of naringenin
2.1. On hypertension
Naringin supplementation turned into observed to enhance hypertension in excessive-carbohydrate/excessive-fats-food plan–fed overweight rats and stroke-inclined hypertensive rats. Moreover, naringin considerably multiplied the manufacturing of Nitric Oxide (NO) metabolic byproducts in urine or rather progressed the acetylcholine mediated endothelium characteristic of the usage of thoracic aortic ring arrangements via way of means of NO manufacturing (4). A comparable vasodilatation effect turned into additionally discovered in excessive-carbohydrate/excessive fats-

food plan–fed overweight rats and streptozotocin-precipitated diabetic rats. Calcium-structured K channels are substantial controller of vascular relaxation. Naringenin activated big conductance Ca2+-activated K+ currents in a concentration-structured way in rat tail artery myocytes (5). Naringenin inhibited TNF-α–precipitated VSMC expansion and shift in a dose-structured way. It additionally blocked the multiplied reactive oxygen species (ROS) are precipitated via way of means of TNFα (4).

2.2. On hyperlipidemia

Naringin supplementation dwindle plasma lipids in speculative fashions of hyperlipidemia or rather weight problems. Naringin supplementation additionally decreased extended plasma lipid concentrations in the excessive-fats-food plan–fed rats and reduced plasma lipids as well as LDL cholesterol in the excessive-LDL cholesterol-food plan–fed rats. The LDL cholesterol-reducing impact of naringin turned discovered in LDL receptor (LDLR) knockout mice (6).

2.3. On obesity

Naringenin promoted gene expression and adiponectin protein secretion from cell line derived from mouse T3 cells (3T3-L1) adipocytes. Naringenin can be beneficial for ameliorating the inflammatory modifications in overweight adipose tissue. It turned into advised that adipose tissue-derived MCP-1, which famous chemotactic home in inflammatory cells, is the important thing for inducing macrophage infiltration into adipose tissue (7).

3. Mechanism of action of naringenin in CVD

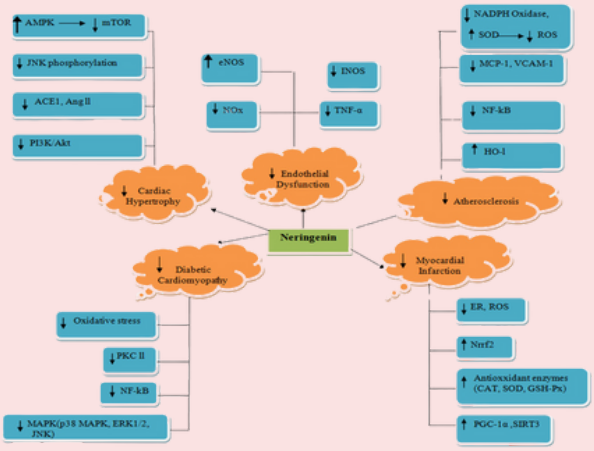

Figure 1. Diagrammatic illustration of the action mechanism of naringenin in various cardiovascular disorders

Abbreviations: ICAM-1, intercellular adhesion molecule-1; ERK, extracellular signal-regulated kinase;CDK, cyclin/cyclin-dependent kinase; VSMCs, vascular smooth muscle cells; eNOS, endothelial nitric oxide synthase;ROS, reactive oxygen species; HW/BW, heart-to-body weight ratio;mTOR, mammalian target of rapamycin: AMPK,AMP-activated protein kinase; LDL, low-density lipoprotein;VLDL, very-low-density lipoprotein;HDL, High-density lipoprotein;MDA, malondialdehyde; CAT, catalase;SOD, superoxide dismutase; GSH-Px, Glutathione peroxidase; HO-1, heme oxygenase; GCLC, glutamate cysteine ligase;Nrf2, nuclear factor erythroid 2-related factor 2;PKCδ, protein kinase C-delta; Akt, protein kinase B; MAPK, mitogen-activated protein kinase; KATP, ATPsensitive potassium;NF-κB, nuclear factor kappa B;NADPH, Nicotinamide adenine dinucleotide phosphate; MCP-1, monocyte chemotactic protein;VCAM1,vascular cell adhesion molecule-1; PKCβII, phosphorylation of protein kinase C βII; ISO, isoproterenol;MI, myocardial infarction; MI/R, myocardial ischemia/ reperfusion; ER, endoplasmic reticulum; ATF6, activating transcription factor 6; PERK, phosphorylation levels of phospho-extracellular regulated protein kinases; IRE1α,inositol-requiring enzyme-1 α; Ang II,angiotensin II; ACE, angiotensin-converting enzyme; apoB, apolipoprotein B; CTGF, connective tissue growth factor; TNF-a, tumor necrosis factor alpha;LVHI, left ventricular hypertrophy index; ANF, atrial natriuretic factor; LV, left ventricle; PPARs, peroxisome proliferator-activated receptors;PGC-1α, peroxisome proliferatoractivated receptor gamma coactivator 1-alpha;iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2.

3.1.Naringenin in atherosclerosis and coronary artery diseases

Hypercholesterolemia is the far more frequently occurring threat play a part for CVD and atherosclerosis (3). Atherosclerosis, as a persistent inflammatory disorder, is defined by the preliminary deposition of lipoproteins inside the vascular endothelium which might be certain and trapped through changed proteoglycans. Naringin restricts vascular smooth muscle cells (VSMC) expansion by stimulating the Ras/Raf/ERK pathway, additionally, effects talked about that ERK signalling is a critical mediator of naringin-triggered suppression of cell growth (8). The outcomes of antioxidant belongings of naringenin in angiotensin II (Ang II)-handled VSMCs had been assessed the use of the rat version of carotid artery balloon harm. The couple of the many vital enzymes accountable for the law of reactive oxygen species (ROS) manufacturing encompass NADPH oxidase and superoxide dismutase (SOD). Naringenin reduced NADPH oxidase pastime and elevated SOD activity, resulting in a significant decrease in the level of Ang II -triggered ROS manufacturing. Furthermore, by limiting the MAPK/NF-B signaling cascade as well as oxygen species pressure, naringenin hindered VSMC expansion and relocation i*n vitro* or rather neointimal granulation tissue formation *in vivo* (9).

3.2. Naringenin and hypertension & cardiac hypertrophy

Heart wreck or failure is a systemic disorder resulting from divergent regulatory mechanisms to make amends for the coronary heart's incapability to pump sufficient blood towards the structures and organs of the human body. Cardiac hypertrophy is a primary hazard issue for coronary heart failure. Several causative elements underlie cardiac hypertrophy, which includes elevated blood pressure, familial hypertrophy, congenital malformations, myocarditis, and dilated cardiomyopathies (4). Many researchers have investigated the outcomes of naringin as well as naringenin in opposition to coronary heart failure in numerous animal models. In *in-vivo* & *in-vitro* models, Park *et al*. assessed the outcomes of naringin remedy on fructose-triggered cardiac hypertrophy and studied the execution of action. Mitochondrial disorder and myocardial ROS manufacturing are suppressed through naringin in cardiomyocytes uncovered to fructose, additionally; cardiomyocyte hypertrophy is reduced through the AMPK/mTOR pathway. Furthermore, it turned into found that fructose-triggered cardiomyocyte apoptosis turned counteracted through naringin via inhibition of ROS-established ATM-mediated p53 signalling pathway. This examination gives a singular method in defensive pathological cardiac hypertrophy for naringin (10).

3.3. Protective outcomes of naringenin as well as naringin in myocardial infarction and ischemic stroke

A very latest examination said that ischemia/reperfusion (I/R) harms impaired cardiovascular features and additionally precipitated mobile apoptosis and MI. Naringenin remedy furnished safety in opposition to I/R harm through stimulating mitochondrial biogenesis and keeping mitochondrial features via the AMPK-SIRT3 signalling pathway. In an examination, the naringin pretreatment protects H9c2 cardiomyocytes from anoxia/reoxygenation (A/R) harm for its functionality to set off the Nrf2 signalling pathway. The information indicated that naringin may want to save you acute myocardial infarction through growing phosphorylation of Protein Kinase C (PKC), which finally activated the Nrf2 signalling. Moreover, the apoptosis price turned into decreased through growing endogenous antioxidative enzymes which include catalase (CAT), superoxide dismutase (SOD), as well as glutathione peroxidase (GSH-Px) (11).

3.4. Benefits of naringenin in opposition to different cardiovascular sicknesses

The lower within side the functioning of the coronary heart is accompanied by fake functioning of mitochondrial failure can increase with age, and the getting old of the coronary heart may also reason apoptosis. The intake of naringenin turned into capable of beautifying the cardioprotective activity. On the report of locating in 1-year-antique rats, naringenin covered the coronary heart via the initiation of mitochondrial large-conductance calcium-activated potassium channel (mitoBK) or rather will discourse cardioprotection in senescent H9c2 cardiomyoblasts (6). Cardiac growing old is frequently resulting from ROS, which includes superoxide radicals as well as hydrogen peroxide (H2O2). Naringenin has a huge ability to grow LDL cholesterol efflux and enhances the lipoprotein profile. Naringenin plays this feature through growing the PI3K/AKT pathway that takes place because of inhibition of ER pressure-ATF6 activity and thereby ensuing in reduced LDL cholesterol efflux in macrophages (9).

3.5. Cardioprotective effects of naringenin and naringin in the diabetic hearts

There is a near affiliation amidst CVD and diabetes mellitus. Heart disorder is the major responsible for fatality in humans with diabetes mellitus. Therefore, focusing on the suitable supervision of hyperglycemia and the well-known remedy of diabetes mellitus and its headaches at the side of control of all CVD chance elements is vital to limit the progression and incidence of diabetes mellitus and CVD. Peroxisome proliferator-activated receptors (PPARs) as nuclear receptors play a huge function within side the remedy of issues along with inflammation, hypertension, dyslipidemia, and diabetes. Narrowly predominant flavonoids for growing PPARs are naringenin which improves diabetes and its headaches along with diabetic cardiomyopathy (12). Naringenin and naringin enhance cardiac characteristics and shape within side the diabetic state. To exhibit the purpose of naringin in cardiac apoptosis in diabetes, the researchers used H9c2 molecular apoptosis below excessive glucose arousal in the way that of an *in vitro* model. Naringin attunes the activity of the p38 signalling pathway and weakens mitochondrial disorder which could cause impedence of cardiomyocyte apoptosis in H9c2 cells in excessive glucose conditions (7). Additionally, naringin facilitates cardiac safety towards the consequences of excessive glucose-caused damage in H9c2 cardiac cells with the aid of using curbing the activation of mitogen-activated protein kinase (MAPK) and oxidative stress pathway (11). Naringenin seems to be worthwhile in diabetic cardiomyopathy with the aid of using raising EETs-PPARs activation and monitoring CYP2J3 protein affirmation in the diabetic cardiac hypertrophy model (12).

Chen, *et al.* manifested anti-apoptotic consequences of naringenin with the aid of using growing HO-1 expression via initiation of Nrf2 in excessive glucose-caused annihilation in human umbilical vein endothelial cells (HUVECs). Naringenin has been proven to grow the affirmation of HO-1, via upregulating Nrf2 as well as PI3K/Akt or JNK signalling pathway (11). Myocardial fibrosis is one of the predominant structural modifications withinside the diabetic hearts which ends up in coronary heart failure (13). A collection of experiments had been achieved within side the hearts of rats with Type 1 diabetes that confirmed naringin regulates the advancement of myocardial fibrosis with the aid of using relieving oxidative stress. The antioxidant ability of naringin ends in the inflection of protein kinase C (PKC)-β and p38 expression, and discount of the potency of NADPH oxidase in cardiac tissue with the aid of using decreasing concentrations of myocardial ROS. There changed into a huge reduction within side the fibrotic vicinity with the aid of using about 67% within side the naringin-treated groups in contrast to the untreated groups (14). Inclined to the consequences of those trials, naringenin and naringin has the ability to deal with CVD coexisting with diabetes.

4. Conclusion

From all the above studies briefed in this article, it is clear that Fat if not consumed in optimum level leads to fatal chronic diseases like CHD, Diabetes and Cancer, including Cardiovascular Diseases. Various bioactive substances have gained a significance to deal with such chronic disorders. To summarize the overall discussion, Naringenin has been manifested to show ameliorative potential against various chronic problems specifically has the ability to interfere in pathways of different CVDs and show targeted mechanisms by which it can rise as a momentous bioactive substance for cardiovascular system as well as related disorders.

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Answers are on page 228

Andrographis paniculata: India's antiviral and immune-boosting answer to rare disease therapeutics


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Abstract
India's phytopharmaceutical industry, built on vast biodiversity and traditional medicinal practices, has spotlighted *Andrographis paniculata* (Kalmegh), known for its potential in rare disease treatment. Traditionally used in Ayurveda and Southeast Asian medicine for ailments like fever, malaria, and diarrhea, *Andrographis paniculata* contains andrographolide—a bioactive compound with anti-inflammatory, antiviral, and immunomodulatory properties. Andrographolide's immune-modulating, anticancer, antibacterial, hepatoprotective, protozoacidal, and antithrombotic effects render it valuable for synthetic pharmaceutical applications, particularly in autoimmune and tropical diseases, as well as cancer therapies. This article explores *Andrographis paniculata's* journey from traditional use to advanced therapeutic applications, emphasizing pharmacological benefits, rare disease potential, and sustainable cultivation. Challenges such as clinical trials, safety, and intellectual property are also considered, with India positioned as a leader in phytopharmaceutical innovation.

Keywords: *Andrographis* paniculata, Phytopharmaceuticals, Andrographolide

1. Introduction

Phytopharmaceuticals, defined as plant-based medicinal products that meet pharmaceutical standards, are an emerging field in India's healthcare and pharmaceutical landscape. With its diverse flora and extensive traditional knowledge, India is uniquely positioned to develop and produce phytopharmaceuticals that address the unmet needs of modern medicine, particularly in the realm of rare diseases (1). Rare diseases, often characterized by limited treatment options and high treatment costs, present significant challenges to healthcare systems (2). Phytopharmaceuticals offer a cost-effective, natural alternative to synthetic drugs, and *Andrographis paniculata* (AP) is a prime candidate in this sector (3).

Given its rich pharmacological profile, *Andrographis* is being studied for its potential to treat conditions ranging from autoimmune disorders to rare infectious diseases (4). India's government has recognized the potential of phytopharmaceuticals and introduced policies to encourage their development and production (5). The Indian Council of Medical Research (ICMR), in collaboration with pharmaceutical companies, is conducting research to bring traditional remedies like *Andrographis* into mainstream therapeutic use (6).

2. *Andrographis paniculata*: From traditional use to synthetic phytopharmaceuticals

Andrographis paniculata, traditionally used for its anti-inflammatory, antipyretic, and hepatoprotective properties, has long been a staple of Ayurvedic and Traditional Chinese Medicine (TCM)(7). However, the plant's transition from a traditional remedy to a modern synthetic phytopharmaceutical involves isolating and synthesizing its bioactive components, primarily andrographolide.

2.1. Botanical profile

Scientific Classification (8):
Kingdom: Plantae
Family: Acanthaceae
Genus: *Andrographis*
Species: A. *paniculata*

2.2. Active phytochemicals

The primary active compound in *Andrographis paniculata* is andrographolide, a diterpenoid lactone that exhibits potent anti-inflammatory, antiviral, and immunomodulatory activities. Other compounds, including neoandrographolide, andrograpanin, and 14-deoxyandrographolide, contribute to the plant's therapeutic effects (9).

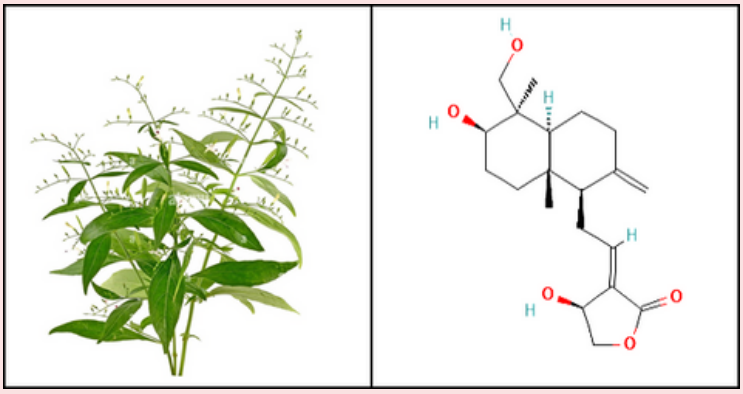

Figure 1. Image of *Andrographis paniculata* plant and chemical structure of andrographolide

2.3. Synthetic derivatives and formulations

To improve the pharmacokinetics of andrographolide, synthetic derivatives are being developed. These derivatives enhance the bioavailability and stability of the compound, making it more effective in treating diseases with chronic or acute inflammatory components. For example, andrographolide nanoparticles have been explored for improved drug delivery and controlled release, particularly in autoimmune and viral diseases (10).

2.4. Bioavailability of andrographolide

Andrographis paniculata, has poor oral bioavailability due to its low aqueous solubility and high lipophilicity**.** This results in limited absorption in the gastrointestinal tract. It is absorbed quickly, reaching maximum concentration in the blood within 1.36 hours, after which it binds extensively to blood proteins and redistributes between tissues. Metabolism of andrographolide occurs mainly in the liver, and its elimination happens through urine and feces**,** with the drug being undetectable after 8 hours (11).

2.5. Pharmacology of andrographolide

Andrographolide works by modulating immune responses through the inhibition of nuclear factor-kappa B (NF-κB), a key regulator of inflammatory cytokines. By downregulating pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, andrographolide can suppress inflammatory responses, making it a potential therapeutic agent for diseases where inflammation is a primary pathological feature (12).

3. Therapeutic potential of *A. paniculata* in rare autoimmune and viral diseases

3.1 Autoimmune disorders

AP has shown significant potential in treating autoimmune disorders, where the immune system mistakenly attacks healthy tissues. Multiple Sclerosis (MS) and Lupus (SLE) are two rare autoimmune diseases where current treatment options are limited, expensive, and often come with severe side effects. Research indicates that andrographolide's ability to suppress the overactivation of immune cells and inflammatory pathways may offer a new therapeutic avenue for these conditions (13).

In MS, a neurodegenerative autoimmune disorder, andrographolide has been observed to reduce neuronal inflammation and protect the central nervous system from damage. Similarly, in Lupus, andrographolide's immune-modulating properties could help control flares and reduce systemic inflammation, a hallmark of the disease (14).

3.2. Cystic fibrosis

Cystic fibrosis, a rare genetic disorder affecting the lungs and digestive system, is characterized by excessive inflammation and mucus buildup in the respiratory tract. Recent studies suggest that andrographolide could mitigate the inflammatory response in the lungs and improve respiratory function, offering potential relief to cystic fibrosis patients (12).

3.3. Tropical diseases

The antimicrobial and antiviral properties of AP make it a candidate for treating rare tropical diseases, such as Leishmaniasis and Dengue fever. Its antiviral mechanisms, which inhibit viral replication and reduce virus-induced inflammation, could be valuable in addressing these neglected tropical diseases (14).

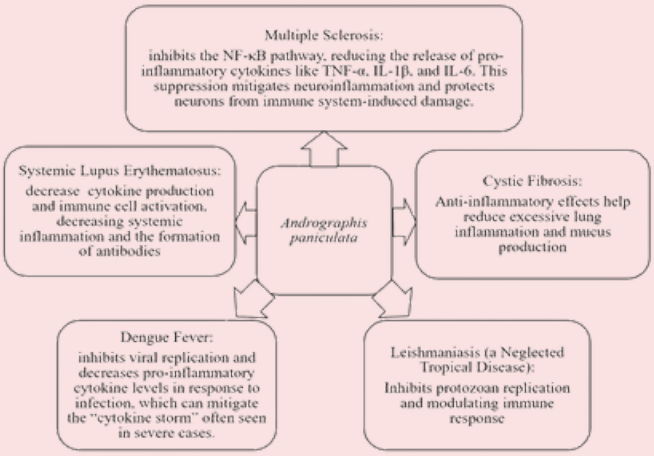

Figure 2. Mechanism of action of *Andrographis paniculata* in various diseases (12-15).

3.4. Cancer therapy

Emerging research also points to the anticancer potential of andrographolide, particularly in inhibiting cancer cell proliferation and inducing apoptosis. These effects are primarily mediated through the suppression of NF-κB signaling and the activation of pro-apoptotic pathways. In addition to targeting multiple pathways to eliminate cancer cells, andrographolide demonstrates a protective effect on normal cells, reducing treatment-induced toxicity-a contrast to its action on cancer cells. This unique profile makes it a promising candidate for further study. Moreover, semi-synthetic analogues of andrographolide have been developed, with some showing significant anti-cancer potential.*Andrographis* may offer an adjunct or alternative therapy for cancers with limited treatment options (15).

Table 1. Key therapeutic mechanisms and clinical applications of *A. paniculata*

S.No.	Action	Mechanism of Action	Biological Target	Clinical Applications	Ref.
1	Antiviral Activity	Inhibits viral entry and replication processes, reduces viral protein synthesis, and interferes with virus maturation stages.	Viral proteases (e.g., 3CLpro in SARS-CoV-2)	SARS-CoV-2, Dengue, Influenza A	(14)
2	Anti-Inflammatory Action	Suppresses NF-κB pathway, reducing pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) and minimizing immune overactivation.	F-κB, MAPK, cytokine signaling	Inflammatory diseases, Cytokine storm reduction, COVID-19, autoimmune disorders	(13)

3	Immunomodulation	Balances immune responses by modulating Th1/Th2 pathways, reducing cytokine storm.	Immune cells (T-cells, macrophages)	Autoimmune diseases, respiratory infections	(13,14)
4	Antioxidant Activity	Reduces oxidative stress by increasing antioxidant enzyme levels, like glutathione peroxidase, and scavenging free radicals.	Reactive oxygen species (ROS)	Cancer, chronic infections, cardiovascular health	(14,15)
5	Apoptosis Induction in Cancer	Activates caspase-dependent pathways, leading to programmed cell death in tumor cells.	Caspases, Bcl-2 family proteins	Targeted cancer therapy, especially hepatocellular carcinoma	(15)
6	Antibacterial Action	Disrupts bacterial cell wall synthesis and inhibits key bacterial enzymes.	Bacterial enzymes (e.g., β-lactamase)	Respiratory, gastrointestinal, and skin infections	(14)

4. Clinical evidence and pharmacovigilance: ensuring efficacy and safety

Clinical trials are crucial in transitioning AP from a traditional remedy to a scientifically validated treatment for rare diseases. In recent years, there have been several clinical trials evaluating its efficacy in conditions like autoimmune diseases, tropical infections, and even cancer (3). Early-phase trials show promise, particularly in reducing systemic inflammation and modulating immune responses, but larger studies are required to confirm these findings (16).

4.1. Pharmacovigilance and safety

Safety is a paramount concern, especially when treating rare diseases where patients often have complex medical conditions. Pharmacovigilance systems must be put in place to monitor the long-term effects of *Andrographis*-based treatments. While generally considered safe at traditional doses, higher doses or long-term use of andrographolide may cause adverse effects, including gastrointestinal discomfort and allergic reactions. Ensuring proper dosing and formulation will be key to minimizing risks (17).

4.2. Nanotechnology-enhanced drug delivery for *Andrographis paniculata*

Nanotechnology offers innovative solutions to improve the delivery of andrographolide (18). Andrographolide-loaded nanoparticles and liposomal formulations are being researched to enhance drug delivery, improve bioavailability, and target specific tissues. These technologies hold promise for more effective and safer administration of *Andrographis*-derived therapies in clinical settings (19).

5. Sustainable cultivation and large-scale production in India

AP is typically cultivated in tropical and subtropical regions of India. The plant thrives in well-drained soils with sufficient moisture and is primarily grown from seeds. Optimal planting occurs between May and July, with recommended spacing of 30 cm x 15 cm to achieve high density and optimal yield. The aerial parts of the plant, particularly the leaves, are harvested between 110 to 130 days after sowing, as they contain the highest concentration of andrographolide, the bioactive compound responsible for the plant's therapeutic properties (20).

As the demand for AP-based drugs grows, ensuring sustainable cultivation becomes critical. India, where the plant grows abundantly, has the potential to become a global supplier of raw materials for pharmaceutical production. Sustainable farming practices not only protect biodiversity but also ensure that large-scale production can meet the needs of the pharmaceutical industry (21).

The Indian government has already initiated programs to promote the cultivation of medicinal plants, including *Andrographis*, under the National Medicinal Plants Board (NMPB). These initiatives focus on organic farming, soil conservation, and biodiversity protection to support long-term sustainability (22).

6. Economic and ecological importance of *Andrographis paniculata* for India

Large-scale cultivation of AP presents significant economic opportunities for rural communities in India. The economic viability of growing *Andrographis*, combined with its ecological benefits, such as promoting soil health and preventing erosion, makes it an ideal candidate for sustainable agriculture (23).

7. Global market opportunities and India's role in *A. paniculata* leadership

The global phytopharmaceutical market is projected to grow exponentially, driven by the increasing demand for natural and plant-based therapies. India is uniquely positioned to become a global leader in the production and export of*Andrographis*-based products, particularly for rare diseases (21).

7.1. Export potential of *Andrographis paniculata*

Countries facing challenges in treating rare diseases, especially in regions with tropical climates, may benefit from importing *Andrographis*-derived drugs. India's ability to provide high-quality, affordable phytopharmaceuticals could make it a key player in the global healthcare market.

7.2. Intellectual property challenges

Securing intellectual property (IP) rights for synthetic derivatives of andrographolide is crucial for India to maintain a competitive edge in the global market. Although traditional knowledge cannot be patented, the process of isolating, synthesizing, and modifying andrographolide (24).

8. Conclusion

Andrographis paniculata emerges as a compelling candidate for treating rare diseases, holding significant promise on both national and global fronts. India's rich agricultural heritage and advanced pharmaceutical capabilities position it to lead the development of synthetic *Andrographis*-based therapies for orphan drug applications. With its natural antiviral and immune-modulating properties, *Andrographis* could transform the treatment landscape for underserved conditions. By leveraging its therapeutic potential, India can improve global health outcomes and stimulate economic growth through large-scale cultivation and export of these innovative phytopharmaceuticals. Collaborative research efforts will be vital to unlocking the full benefits of this powerful natural remedy.

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Herbal innovations: Phytopharmaceuticals as India's next big pharma frontier

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Abstract
India, with its rich heritage in traditional medicine, particularly Ayurveda, Siddha, and Unani, is positioned uniquely in the global pharmaceutical landscape. The concept of phytopharmaceuticals-medicines derived from plant sources—represents a significant shift towards integrating traditional knowledge with modern science. This article explores the current state of the herbal pharmaceutical industry in India, the innovations in phytopharmaceutical research, the regulatory frameworks shaping this sector, and the economic potential of herbal innovations. With an increasing global demand for natural remedies, India stands at the forefront of this burgeoning industry, making phytopharmaceuticals a critical frontier for future pharmaceutical developments.

Keywords: Plant-based Medicines, Traditional Knowledge, Modern Science, Herbal Pharmaceutical Industry, Phytopharmaceutical Research

1. Introduction
India has a long-standing tradition of using herbal medicine, with its roots deeply embedded in ancient systems like Ayurveda. As global health trends shift toward natural and plant-based therapies, the phytopharmaceutical sector is gaining momentum. Phytopharmaceuticals are defined as products derived from medicinal plants, scientifically validated for their therapeutic efficacy and safety. This article delves into the evolution of herbal innovations in India, highlighting the intersection of traditional practices and modern scientific research, and how this synergy can lead to the development of safe and effective phytopharmaceuticals (1,2). The main steps involved in bringing herbal innovations from traditional or scientific research stages to commercial availability are shown in Figure 1.

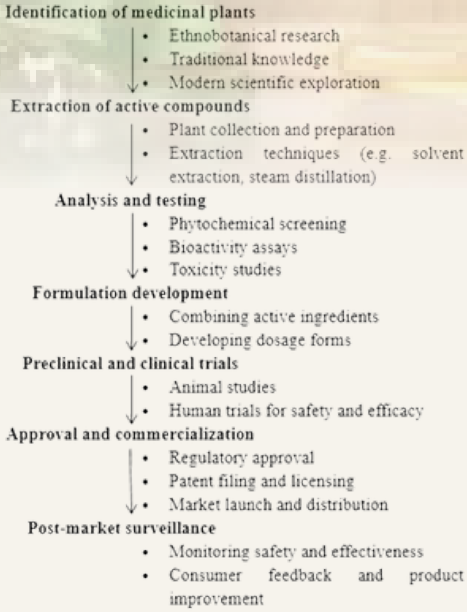

Figure 1. Steps to commercialise herbal innovations from traditional or scientific research

2. Traditional systems of medicine in India

India's traditional medical systems, particularly Ayurveda, are among the oldest in the world. Ayurveda, often described as a holistic approach to health, emphasizes the balance of mind, body, and spirit. It utilizes a wide variety of herbs, plants, and minerals, believing that natural substances can promote health and prevent disease. Similarly, Siddha and Unani systems have their unique methodologies and therapeutic approaches, contributing to India's rich tapestry of traditional healing practices.

Historically, these systems have relied on empirical knowledge passed down through generations. However, the recent integration of scientific methods into the study of herbal medicine has paved the way for the development of phytopharmaceuticals. By validating the medicinal properties of plants through rigorous research and clinical trials, India can effectively bridge the gap between ancient wisdom and modern medicine (3,4).

Table 1. Summary of the traditional systems of medicine in India

S.N.	System of Medicine	Origin Period	Key Principles	Main Therapies	Key Texts	Practitioners/ Title	Key Formulations/ Medicines
1.	**Ayurveda**	2,500 BCE (Ancient)	Balance of doshas (Vata, Pitta, Kapha)	Herbal medicine, Panchakarma, Yoga	Charaka Samhita, Sushruta Samhita	Vaidya	**Chyawanprash** (immune-boosting tonic) **Ashwagandha** (adaptogen, stress relief)
2.	**Unani**	8th Century (Islamic)	Balance of humors (Dum, Balgham, Safra, Sauda)	Herbal treatment, Massage, Cupping	Canon of Medicine, Al-Qanoon fi al-Tibb	Hakim	**Majun** (or Majun) **Mulayyan** (digestive and laxative) **Cinnabar** (for respiratory and digestive issues)
3.	**Siddha**	Ancient, similar to Ayurveda in the Tamil region	Balance of humors (Vaatham, Pittam, Kapam)	Herbal, minerals, Yoga	Agattiyar texts	Siddhar	**Kabasura Kudineer** (for immune support and fever) **Eladi Churnam** (for digestive issues and respiratory problems)
4.	**Yoga and Naturopathy**	Ancient	Physical, mental, spiritual harmony	Yoga, Pranayama, Mudras, Hydrotherapy	Patanjali's Yoga Sutras	Yoga therapist, Naturopath	**Turmeric** (anti-inflammatory, antioxidant) **Triphala** (used in detox programs)
5.	**Homeopathy**	19th Century (Germany)	Similia similibus curentur (Like cures like)	Potentized medicines, Diet	Organon of Medicine	Homeopathic Doctor	**Arnica montana** (for injuries, bruises, and trauma) **Oscillococcinum** (for flu-like symptoms)

3. The emergence of phytopharmaceuticals

3.1. Phytopharmaceuticals

Phytopharmaceuticals are products derived from plants that contain active ingredients intended for therapeutic use. Unlike traditional herbal remedies, which may lack standardization and scientific validation, phytopharmaceuticals undergo extensive research and testing to ensure their efficacy, safety, and quality. These products are often formulated as extracts, powders, or capsules, allowing for more precise dosing and administration (5).

3.2. Global trends in phytopharmaceuticals

The global phytopharmaceutical market is witnessing significant growth, driven by increasing consumer awareness and demand for natural health products. The shift away from synthetic drugs, largely due to concerns about side effects and long-term health impacts, is propelling the popularity of herbal alternatives. A report by Fortune Business Insights estimates that the global phytopharmaceutical market will reach USD 45 billion by 2027, growing at a CAGR of 7.6%. This trend is particularly pronounced in developed markets, where consumers are seeking holistic and preventive health solutions (6).

In India, the growing diabetic population, rising incidence of lifestyle diseases and increasing interest in preventive healthcare are driving the demand for phytopharmaceuticals. Traditional herbs such as Ashwagandha, Turmeric, and Brahmi are being recognized for their therapeutic properties, leading to a burgeoning industry focused on research, development, and commercialization of herbal products (6).

4. Key innovations in Indian phytopharmaceuticals

4.1. Ethnopharmacology and the role of traditional knowledge

Ethnopharmacology is the study of the medicinal properties of plants as used in traditional cultures. In India, ethnopharmacological research plays a crucial role in identifying new phytopharmaceuticals. Many of the country's indigenous communities possess a wealth of knowledge about local flora and their therapeutic applications. Collaborations between ethnobotanists and local healers are critical in documenting these practices and validating them through scientific methods.

Case Study: Turmeric *(Curcuma longa*)

One of the most celebrated phytopharmaceuticals is turmeric, which contains curcumin, a compound with potent anti-inflammatory and antioxidant properties. Turmeric has been used in Ayurveda for centuries to treat various ailments, including arthritis, digestive disorders, and skin conditions. Modern research has corroborated these traditional uses, with numerous studies highlighting curcumin's efficacy in managing chronic diseases such as cancer and cardiovascular diseases. The commercialization of standardized curcumin extracts exemplifies how traditional knowledge can inform modern drug development (7).

4.2. Biotechnological advancements

The integration of biotechnology into herbal medicine is revolutionizing the development of phytopharmaceuticals. Techniques such as tissue culture, molecular breeding, and genetic engineering are being employed to enhance the yield and potency of medicinal plants. For instance, tissue culture allows for the mass propagation of rare or endangered medicinal species, ensuring a sustainable supply for research and commercial use.

Example: Ashwagandha (Withania somnifera)

Ashwagandha, known for its adaptogenic properties, is traditionally used to combat stress and enhance vitality. Biotechnological approaches have been utilized to increase the concentration of bioactive compounds in Ashwagandha, thereby enhancing its therapeutic potential. The successful commercialization of high-potency Ashwagandha extracts highlights the importance of scientific innovation in the herbal sector (8,9).

4.3. Nano-phytopharmaceuticals

Recent advancements in nanotechnology have opened new avenues for phytopharmaceutical development. Nano-phytopharmaceuticals utilize nanocarriers to enhance the bioavailability and targeted delivery of herbal compounds. This approach can significantly improve the effectiveness of herbal medicines, addressing challenges related to solubility and absorption.

Application: Curcumin nanoparticles

Curcumin nanoparticles are an emerging area of research, offering enhanced bioavailability compared to conventional curcumin formulations. Studies have shown that these nanoparticles can improve curcumin’s anti-inflammatory and anticancer properties, making it a promising candidate for treating chronic diseases. This innovation exemplifies how combining traditional knowledge with cutting-edge technology can lead to breakthroughs in phytopharmaceutical development. Curcumin’s mechanisms of action are broad and multifaceted. It influences inflammatory pathways, oxidative stress, gene expression, and cellular signalling, thereby exerting therapeutic effects across a variety of conditions. Whether it's by modulating the NF-κB and COX-2 pathways to reduce inflammation, activating Nrf2 to enhance antioxidant defences, or inducing apoptosis and cell cycle arrest in cancer cells, curcumin offers a powerful means of improving health across different systems of the body (8,9).

5. Regulatory framework for phytopharmaceuticals in India

5.1. Government initiatives and policies

The Government of India has recognized the potential of phytopharmaceuticals and has implemented

various initiatives to promote their development. The National AYUSH Mission aims to promote the growth and development of traditional medicine systems, including Ayurveda, Yoga, Unani, Siddha, and Homeopathy.

5.2. Phytopharmaceutical guidelines (2015)

In 2015, the Central Drugs Standard Control Organization (CDSCO) released guidelines for the registration and approval of phytopharmaceuticals. These guidelines establish a clear regulatory pathway for herbal products, requiring manufacturers to adhere to strict standards for quality, safety, and efficacy. This regulatory framework is essential for building consumer trust and encouraging investment in the sector (10,11).

5.3. Quality control and standardization

Quality control is a critical aspect of phytopharmaceutical development. Unlike synthetic drugs, herbal products often vary in composition due to factors such as geographical location, climate, and harvesting techniques. To address this, manufacturers are adopting standardization practices, which include:

- Phytochemical profiling: Analyzing the chemical constituents of herbs to ensure consistent quality.
- Good Manufacturing Practices (GMP): Implementing strict manufacturing protocols to maintain product quality and safety.

The establishment of quality control laboratories and research institutions dedicated to phytopharmaceuticals is crucial in ensuring that these products meet international standards (12).

6. Economic potential and global market trends

6.1. Market growth and opportunities

The global demand for herbal products is rapidly increasing, and India is well-positioned to capitalize on this trend. The Indian herbal market is projected to reach USD 20 billion by 2025, driven by rising consumer awareness and preference for natural remedies. This growth presents numerous opportunities for both established companies and startups in the phytopharmaceutical sector.

6.2. Export potential

India's rich biodiversity and traditional knowledge base offer significant export potential for phytopharmaceuticals. Countries in Europe and North America are increasingly sourcing herbal products from India, driven by consumer demand for natural health solutions. The Indian government is actively promoting the export of herbal products through initiatives such as the Make in India campaign, which aims to enhance manufacturing and global competitiveness (13,14).

6.3. Investment in research and development

Investment in research and development is crucial for the growth of the phytopharmaceutical industry. Collaborations between academic institutions, research organizations, and the private sector can drive innovation and enhance product development. The establishment of dedicated research centres focusing on phytopharmaceuticals can facilitate the discovery of new drugs and the optimization of existing formulations. The National Medicinal Plants Board (NMPB) is a body established by the Government of India to promote the sustainable development, conservation, and cultivation of medicinal plants across the country. The board functions under the Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy) and plays a vital role in supporting traditional medicine systems and promoting the use of medicinal plants.

7. Challenges facing the phytopharmaceutical sector

7.1. Standardization issues

One of the primary challenges facing the phytopharmaceutical sector is the lack of standardization.Variability in the chemical composition of herbal products can lead to inconsistent therapeutic effects. Establishing standardized extraction and formulation processes is essential for ensuring product quality and safety.

7.2. Regulatory hurdles

While the Indian government has made strides in establishing regulatory frameworks for phytopharmaceuticals, navigating these regulations can be complex for manufacturers. Streamlining the approval process and providing clear guidelines for product registration is crucial for fostering growth in the sector (15).

7.3. Consumer awareness and education

Despite the growing popularity of herbal products, many consumers remain unaware of the differences between traditional herbal remedies and scientifically validated phytopharmaceuticals. Education and awareness campaigns can help bridge this knowledge gap, promoting informed consumer choices and building trust in herbal medicines (16).

8. Future directions and innovations

8.1. Integration of traditional and modern medicine

The future of phytopharmaceuticals lies in the integration of traditional and modern medical practices. By leveraging the rich knowledge of traditional systems and the rigor of scientific research, India can develop innovative products that meet the needs of modern healthcare.

8.2. Sustainability and conservation

As the demand for medicinal plants increases, sustainability and conservation of biodiversity must be prioritized. Implementing sustainable harvesting practices and supporting the cultivation of medicinal plants can ensure a consistent supply for phytopharmaceutical development.

8.3. Global collaborations

Collaborations with international research organizations and pharmaceutical companies can facilitate knowledge exchange and promote the global reach of Indian phytopharmaceuticals. Participating in global forums and trade shows can also enhance visibility and foster partnerships in the international market (17).

9. Conclusion

India stands at the forefront of the phytopharmaceutical revolution, with its rich tradition of herbal medicine and growing scientific advancements. The convergence of traditional knowledge and modern technology has the potential to unlock new therapeutic avenues, making phytopharmaceuticals a vital component of the future healthcare landscape. By addressing challenges related to standardization, regulation, and consumer education, India can solidify its position as a global leader in the herbal innovation space. As the world increasingly embraces natural remedies, the phytopharmaceutical sector offers immense opportunities for growth, development, and improved health outcomes.

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The regulatory framework for phytopharmaceuticals

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Abstract

Phytopharmaceuticals, classified as purified and standardized plant-based drugs containing multiple bioactive compounds, are emerging as a vital category in modern medicine. In India, the regulatory framework for these drugs, overseen by the Central Drugs Standard Control Organization (CDSCO), ensures that phytopharmaceuticals meet stringent standards for quality, safety, and efficacy, similar to synthetic drugs. This approach contrasts with traditional AYUSH medicines, as phytopharmaceuticals emphasize scientific validation and standardization of plant materials. The introduction of regulatory provisions through the Drugs and Cosmetics Act (D and C Act) supports the development of botanical-based drugs, fostering innovation in the field. Phytopharmaceuticals promoting their acceptance in the global market and encouraging research into plant-derived therapeutics. This regulatory framework presents a promising avenue for the integration of traditional knowledge with modern science, advancing the development of effective, plant-based therapies.

Keywords: Regulatory, Ophthalmic drugs, Safety, Standardization, Bioactive

1. Introduction

Phytopharmaceuticals are characterized by the purification and production of fractions containing at least four bioactive or phytochemical compounds that have been well and quantitatively evaluated. These drugs are obtained from the extraction of medicinal plants or their parts and are intended for internal or external use by humans or animals. Their purpose includes the diagnosis, treatment, cure or prevention of diseases or conditions unless administered parenterally (1-3).

2. Regulatory framework and standards for phytopharmaceuticals in India

Phytopharmaceutical drugs in India come under the supervision of the Central Drugs Standard Control Organisation (CDSCO), which grants special approval to these products. The gazette notification outlines the need for scientific data on efficacy, safety and effectiveness to ensure that herbal medicines, similar to synthetic drugs, are rigorously evaluated. This equation contrasts traditional medicine, which is often viewed with suspicion, with traditional AYUSH medicine, which has long relied on herbal medicines. Herbal medicine refers to the reusability and standardization of plant materials used in the development of medicine while embracing traditional knowledge. The extracts are standardized, measured and qualitatively assessed. These drugs are obtained from medicinal plants and are intended for use in diagnosing, treating, alleviating or preventing diseases or disorders in humans or animals, but do not include parenteral administration (3-5).

In Schedule Y, the newly added Annex I B specifies the information required for medicinal practices or the import and manufacture of herbal medicines in India. Regulatory requirements for new drug applications (NDAs) for botanicals include standard procedures such as safety data, drug data, and human studies including clinical trials. Additional emphasis is given to: Information on botanical origin, formulation, route of administration, dosage, therapeutic class, and drug claims procedure. Once approved by the CDSCO, these drugs will have the same commercial status as compounded drugs under international regulations in countries such as the United States and China. This change encourages scientific research, innovation, and the creation of new herbal medicines, thus promoting greater acceptance of herbal products in modern medicine (6-12).

Acts D and C of October 24 establish the regulatory framework for the identification and approval of herbal medicines. This policy includes the scientific evaluation of herbal medicines (similar to synthetic drugs). Although this policy is not yet in force, some botanical products such as Guggulu tablets (for hypercholesterolemia), Ginkgo biloba leaves (for memory loss) and silymarin capsules (for liver disease) have been found to do well by the CDSCO. However, the approval process for these products is taking a long time due to the need to make regulators aware of the unique challenges faced by botanicals compared to synthetic products (13-15).

Especially medicines derived from traditional knowledge such as Ayurveda, which has a long history of safe use. In August 2008, the Government of India appointed Nitya Anand and DBA Narayana as interlocutors to consider these policies. The expert panel emphasized the importance of creating herbal medicines inspired by Ayurvedic wisdom but measured against modern science. It does not affect the application of Ayurvedic, Siddha and Unani (ASU) medicines subject to Section IVA. These regulations provide another avenue for the development of botanical medicines, support scientific research and drug development, and allow ASU products to continue to be managed under the same criteria that are already there (16,17).

3. Standardization and characterization of phytopharmaceuticals

Standardization of botanical medicine includes detailed information about herbal products including inspection of harvesting areas, growing and processes such as washing, drying and storage. Other important factors include certification of herbal products, presence of phytotoxins and tests such as sensory evaluation, ash value and microbial count.

According to Indian Pharmacopoeia (2014), the extraction process should be adjusted within a certain tolerance according to the biomarker or drug marker content. Similarly, the United States Pharmacopoeia (USP) and the European Pharmacopoeia provide guidelines for the standardization of botanical products to ensure efficacy and therapeutic effectiveness (18,19).

4. Integrated approach and global alignment

The development of plant medicine requires an integrated approach that draws on traditional knowledge, modern scientific data, bioassays, and decisions such as biodiversity and international management. Plant-based phytopharmaceuticals comply with national regulations, such as those in the United States and China, to ensure that these products are scientifically evaluated and not based on traditional knowledge.

This policy encourages innovation in medicine, especially for industry and scientists working on plant-based lead. With well-controlled clinical trials to maintain safety and efficacy measures, botanical drugs can be expected to gain wider acceptance in today's medical community. The Drugs Inspector General of India considers these drugs to be similar to synthetic drugs and wants to expand their use and encourage more research in this area.

The botanical medicine research initiative responds to the global interest in phytotherapeutics and has the potential to address unmet medical needs and lead to future change (20,21).

5. Limitations of phytopharmaceuticals

The development of phytopharmaceuticals faces major challenges, especially for small and medium-sized enterprises (SMEs) facing financial constraints. The significant costs of clinical trials, international certification and international product registration all require significant financial support.

Additionally, lack of regulatory oversight hinders progress in scientific research needed to develop effective, evidence-based herbal medicines. Complex and restrictive patent laws are a barrier to innovation and business growth. The Biodiversity Act of 2002 adds an additional layer of complexity that impacts current and future development in the phytopharmaceutical sector (17,19).

6. Requirements for submission of application for clinical trials, import, or manufacture of a phytopharmaceutical drug

6.1. PART I: Data to be submitted by the applicant

- **6.1.1. Medical information:** A brief summary of the botanical drug, including botanical name (by use or spelling), composition, application, dosage, medical classification, and administration schedule.
- **6.1.2. Published literature**: Documented information on the use of plants or drugs in traditional or ethnomedicine, including licenses and information on ingredients, dosage, and administration.
- **6.1.3. Contraindications and side effects**: Information from traditional or current use indicating known contraindications, side effects, or adverse reactions.
- **6.1.4. Research reports:** Published studies on the safety and medicinal properties of drugs. This should include: Information on normal use or procedures.
- **6.1.5. Usage history**: Information on current use including details of the product, manufacturer, sales, human exposure and duration on the market.
- **6.1.6. Pharmacological information**: Information on pharmacodynamics, clinical studies and human trials (if applicable).
- **6.1.7. Monographs**: A monograph of a plant, product or extract with English translation is required (17,19,23).

6.2. PART II: Data generated by applicant

- **6.2.1. Identification and origin of plant material:** Taxonomic description with botanical name (genus, species, family) followed by evidence and confirmation by a taxonomist.
- **6.2.2. Operation and handling:** Details of plant growth, harvesting stages, harvesting techniques, drying, storage and transportation. This will also include details of collision, inspection and finishing of small parts.
- **6.2.3. Quality characteristics:** Foreign products, ash, pesticide residues, heavy metals, microbial content and chromatographic fingerprints. testing procedures and quality control procedures.
- **6.2.4. Extraction process:** Detailed extraction and fractionation process, good properties of the starting material, physical examination and physical and chemical allergies.
- **6.2.5. Production and final product:** Detailed information on the composition and proportion of the purified product.
- **6.2.6. Manufacturing process:** Description of the manufacturing process for the pharmaceutical form, including environmental controls, in-process quality control, and volume details.
- **6.2.7. Stability data:** Stability testing at various conditions (e.g., 40°C and 75% RH) for both the phytopharmaceutical drug and its dosage form, monitored over specific time periods.
- **6.2.8. Safety and toxicity data:** Animal toxicity data (28- to 90-day repeated dose oral toxicity studies). Investigation for teratogenicity (if the drug is intended for use during pregnancy).
- **6.2.9. Clinical studies:** Clinical studies were conducted in accordance with the rules and guidelines used for new drugs. This includes: Phase I studies to determine the maximum antibiotic dose and toxicity. The safety of the test is short.

6.2.10. **Regulatory and commercial information:** Status of botanical medicines in other countries, regardless of whether they are classified as food, dietary supplement or approved drug. Detailed information on packaging, labelling and post-marketing surveillance plans, including regular safety updates.

6.2.11. **Other important information:** Other details about herbal medicines under regulatory authority. These include substances such as carotenoids, flavonoids, terpenoids, omega-3, fatty acids, etc. (17,19,22,23).

7. Conclusion

The regulation of phytopharmaceuticals encourages the development of plant-based drugs using modern techniques such as solvent extraction and advanced formulation. With approval from regulatory bodies like CDSCO, these products can be marketed as new chemical entity-based drugs. This regulatory framework aligns with global standards, promoting innovation and investment in phytopharmaceutical drug development.

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Phytopharmaceutical industry in India: An insight towards its growth and sustenance

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Abstract

Advancements in technology coupled with versatility in healthcare approaches led to the rise of a section of herbal medicines called phytopharmaceuticals. The paper presents some factors that affect the scope for rise of phytopharmaceutical industry in India like industrial crops sector and trade, richness of Indian herbal resources, cultivation advantage and government schemes to support development of phytopharmaceuticals. Environmental hazards, loss of biodiversity, plant disease issues, and genetic erosion can occur during the collection and processing of herbs for phytopharmaceuticals. Thus the paper further lists some approaches that can be adopted to sustain the industry e.g. CRISPR technology, DNA barcoding, metabolic engineering, hydroponics, ultra sound assisted/ supercritical fluid based extraction.

Keywords: Phytopharmaceuticals, Industry, Sustainability, Regulation

1. Introduction

The Indian Pharmacopoeia (IP) has monographs segregated into various sections one of them being herbs and herbal products. It is noteworthy that in the 8th edition published in 2018 there was a section on herbs and herbal products but in the 9th edition published in 2022 the IP saw an added section of monographs titled 'Phytopharmaceuticals'. Seven monographs that were in the section 'Herbs and Herbal Products' have been moved into the new section of Phytopharmaceuticals (e.g. Henna). The monograph title bears the suffix 'PPI' e.g. *Lawsonia inermis* PPI for henna. Haridra has been titled as Curcuma longa PPI (1). This upgrading in the official book of standards two years ago, for which the monograph drafting must have commenced much earlier indicates the importance of phytopharmaceuticals (PP) and their immense potential for India.

Herbal medicine is booming as a promising approach healthcare management of the future. Herbs serve as cure for several ailments and have a long established traditional use and a historic background (2). Historical records of China, Egypt and India indicate the medicinal applications of plants as far back as 3000 BC. Ayurveda, Siddha, Arabic Unani Medicine, and Traditional Chinese Medicine, employ herbal therapies (3). With the awareness of adverse effects related to synthetic drugs, many individuals are resorting to herbal remedies (4). Herbal medicinal products encompass a

variety of items, including herbs, herbal materials, herbal preparations, and finished herbal products. These products contain parts of plants, other plant-derived materials, or combinations of these as their active ingredients (5).

A phytopharmaceutical drug is a standardized and purified fraction of an extract of a medicinal plant or its part that contains at least four bioactive or phytochemical compounds (as determined by qualitative and quantitative methods). It can be used internally or externally by humans or animals for the diagnosis, treatment, mitigation, or prevention of any disease or disorder; however, parenteral administration is not included in this definition (e.g. atropine, caffeine, ephedrine, quinine, etc.) (6,7). There is not much difference between PP, nutraceuticals, and functional foods, it is majorly based on the on the preparation, dosage, and other variables, certain plants and their constituents is used in all of the above formulations (8).

2. Market size of phytopharmaceuticals

Plant extracts market referring to the PP market was valued at 33.9 billion USD in 2022 and is predicted to be 94.1 billion USD by 2031 with a projected growth rate of 12% for 2023-2031 (9). The numbers vary slightly based on different surveys but all of them show a rise in the demand for PP. According to FMI's analysis, India's phytochemical market is projected to expand at a CAGR of 6.2% between 2023 and 2033. USA, Germany, UK, Spain China are also on the list towards expansion of their markets (10). The end user the application of PP is so diverse which is the driving their demand. They are used not only in medicines and nutraceuticals but also in foods, beverages, personal care products, nutircosmetics, vegan products.

Some key players in the phytochemical market Include Döhler GmbH – Germany, Naturex -France, Kemin Industries Inc USA, Linnea SA – Switzerland, Sabinsa Corporation – USA, Kothari Phytochemicals & Industries Ltd- India, Indena SpA – Italy, Alkaloids Corporation – India, Arboris LLC -USA , Allied Biotech Corp.- Taiwan, Organic Herb Inc. (OHI) – China and LIPO Foods France (10). Some more Indian companies include Phyto Life Sciences Pvt Ltd: S. G. Phyto Pharma Pvt. Ltd and Blumen. A few others are Bionics Remedies, Wilson Drugs, Navayur Herbal, Indian Herbo Pharma, Alrak Ayurveda, Medlock Healthcare, Gnova, and Biosync Pharma (11).

3. Prominence of India in the phytopharmacetical industry

India serves to be a promising source of herbal drugs for many reasons such as the abundance in the herbs and herbal products; the herbs used in the traditional system of medicine contain reference in many Pharmacopoeias which guide for acquiring the standard quality of the herbs and their formulations. Some aspects affecting PP industry India are listed below projecting their pros and cons.

3.1. Industrial crops and trade

Plants are used as industrial crops as volatile oils, pharmaceuticals, herbal health products, personal care products, dyes and colorants, semisynthetic derivatives, biopesticides etc. Majority of plants are collected from wild source as against cultivation. The crops with much value and being cultivated are, *Papaver somniferum L, Catharanthus roseus, Aloe* species *, Commiphora wightii, Atropa belladonna L, Strychnosnux-vomica Linn., Solanum* species, *Emblica officinalis, Cassia angustifolia Vahl., Plantago ovata Forsk., Stevia rebaudiana, Coleus forskohlii, Acorus calamus, Ocimum sanctum Linn.* (12). Medicinal plant species are traded in China and India. As per a 2021 annual global trade in. herbal medicines of over $100 billion, China and India account for about $2–5 billion of this trade (13).

Alternative medicine, including Indian Ayurveda, Unani Arabic remedies, and Traditional Chinese Medicine, is beginning to gain popularity in affluent nations and gain more respect in other nations. According to WHO forecasts, the need for medicinal plants will rise to by USD 5 trillion 2050 (14). Research studies on industrialization of medicinal plants would need thorough data on their production, usage, commercialization, and management (15,16). It may be noted that though India is lucrative for the PP industry, there could be a competition from other Asian and Western nations.

3.2. Potential source of raw materials

About 70% of Indian medicinal plants are found in tropical regions, primarily in forests across the Western and Eastern Ghats, the Vindhyas, the Chotta Nagpur Plateau, the Aravalis, and the Himalayas. About 20% of all plant species worldwide (about 45,000 species) are found in the Indian subcontinent. Less than 30% of the medicinal plants with strong medical potential are found in temperate, alpine, or higher elevation environments (17). Less than 20 plant species (approximately 2.5%) are being grown out of the more than 800 plant species used by the herbal business. Over 90 % of medicinal plants in India are harvested from the wild using extremely antiquated and damaging methods which are linked to habitat degradation, overexploitation, changes in land use, threat to genetic diversity and species survival (18). The products from the wild are decreasing in the long run due to the genetic erosion. Measures are necessary to promote trade and homogeneity while simultaneously guaranteeing safety and accuracy (19,20). This scenario of genetic erosion is analogous to India as well.

3.3. Cultivation potential of India

India has an immense potential towards cultivation of medicinal plants with some hurdles as listed in Table 1 (21,22, 23) Key medicinal plants being cultivated are Ashwagandha (*Withania somnifera*), Tulsi (*Ocimum sanctum*), Aloe Vera *(Aloe barbadensis)* and Safed Musli (*Chlorophytum borivilianum*).

Table 1. Advantages and disadvantages of cultivation of medicinal plants in India

Advantages	Disadvantages
15 agro climatic zones that suit a large variety of plants.	Lack of Technical Knowledge on best practices for cultivation and management
Cultivation alleviates pressure on wild populations	Quality threats due to sustitutes and adulterants, affecting product quality.
Biodiversity conservation facilitated	Climatic challenges which affects the product yield
Traditional cultivation methods e.g. with Bhotiya of Himalayas, adapted for commercial use proved economical and preserved indigenous medicinal knowledge	Unregulated supply chain complicates market dynamics and quality assurance

3.4 Government schemes

A new set of laws for “Phytopharmaceutical drugs” was announced by the Indian government in 2013 as an amendment to the Drugs and Cosmetics Rules 1945. These regulations specify and clarify the prerequisites for Indian PP medications. In order to assess and approve the marketing of a plant medication on par with synthetic, chemical moieties, this gazetted notification governs the definition, regulatory regulations, and submission criteria for phytopharmaceutical medications, including scientific data on quality, safety, and efficacy. The Indian Govt. is inclined to support the pharma industry which includes the PP as well. Production Linked Incentive (PLI) scheme and Scheme for promotion of research and innovation in pharma medtech sector (PRIP) support manufacturing and research in the PP industry in India have allocated funds for the same (24,25).

Thus with its rich heritage of traditional medicine, vast biodiversity, plenty of forest area and cultivable land, availability and accessibility of labour and technology, skilled workforce, government support, the PP industry in India is gaining importance.

4. Sustainability of phytopharmaceuticals industry

Sustainability is defined as the ability to maintain or improve the state and availability of desired resources over a long period of time. Sustainability usually has three dimensions (or pillars): social, environmental, economic. However, the environmental dimension is mostly emphasized. This includes addressing key environmental problems, including climate change and biodiversity loss (26).

Sustainable practices in PP are crucial for ensuring the long-term availability of medicinal plants and minimising environmental impact. Here are some key strategies:

- Developing sustainable supply chains to ensure a constant supply of medicinal plants and replenishing of resources (27).
- Adopting green chemistry and green technology to reduce the carbon footprint.
- Regulation, Government policies and Community involvement to ensure prevention of overharvesting and unscrupulous trading and overexploitation.

4.1. Supply chain of raw materials

This includes ensuring a constant supply of raw materials i.e. herbs. This can be achieved in several ways like, practising sustainable harvesting techniques both from the wild and cultivated sources, adopting conservation methods: in situ and ex situ, like seed banking, gene banking and cryopreservation, promoting cultivation of medicinal plants and adopting good agricultural practices (GAP), creating alternate sources of medicinal plants from techniques like vertical farming, hydrophonics, aerophonics, tissue culture, biotechnology, and investing in research and development activities to explore latest developments in the field (28-30).

- CRISPR/Cas9 Gene Editing facilitates enhancement of the traits of medicinal plants, like diseases and pests resistance thus aiding higher yields and reduced need for chemical inputs.
- Metabolic Engineering: helps modify the metabolic pathways of plants to raise the production of desired phytochemicals, making the extraction more yielding.
- DNA Barcoding helps to use genetic markers to accurately identify and catalogue medicinal plant species, thus suitable for monitoring and protecting biodiversity.
- Tissue Culture, Hydroponics, and Biotechnology when integrated into the cultivation of medicinal plants is transforming traditional practices and enhancing sustainability. These modern techniques address challenges such as overharvesting, climate change, and the need for consistent quality in medicinal plant production (31).

4.2. Reduction of carbon footprint and water foot print

This includes implementation and adoption of various strategies like choosing eco-friendly materials e.g. the packages that are employed in the PP industry (31). Optimizing manufacturing processes by eco-friendly extraction methods like:

- **Supercritical fluid extraction (SFE):** Using supercritical CO2 as a solvent to extract phytochemicals, which is more environmentally friendly compared to traditional solvent extraction methods.
- **Ultrasound assisted extraction (UAE):** Utilizing ultrasonic waves to enhance the extraction efficiency of bioactive compounds, reducing the need for harsh chemicals.

Optimizing waste management wastes segregation and disposal to prevent pollution, ensuring recycling and replenishing water resources to ensure water conservation and use of using renewable energy sources.

5. Conclusion

Phytopharmaceuticals are employed in pharmaceutical products, foods, beverages, cosmetics, nutraceuticals, wellness products, teas, etc. India has an advantage due it geographical, technological, human resource features, ecological factors. Not only forest based but also the availability of a marine ecosystem provides diverse vast and versatile drugs. But if the natural resources are being exploited unhindered, right from the source of phytopharmceuticals, to its processing and delivery as a finished pharmaceutical product, the depletion of soil, loss of biodiversity, reduced yields may occur. Thus though India has immense potential in the phytopharma industry, measures have to be taken to ensure that there is continued growth and progress by ensuring the environment is not adversely affected due to the reliance on plants for medicines and employment of organic solvents for isolation and extracting the phytoactives. Sustainability practices not only help in conserving medicinal plants but also ensure that the benefits of phytopharmaceuticals can be enjoyed by future generations.

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PHARMA NEWS ROUND-UP

06th September, 2024: In a move to reduce India's dependency on China and as part of the Production Linked Incentive scheme, the Department of Pharmaceuticals, India has announced that India will soon start domestic production of bulk drugs, Penicillin G and Clavulanic Acid which is a key ingredient in the antibiotic Augmentin.

11th September, 2024: Bharat Biotech has collaborated with Alopexx, Inc. for the co-development and commercialisation of AV0328 synthetic vaccine. It is the Alopexx, Inc.'s proprietary broad-spectrum anti-microbial vaccine targeting poly N-acetyl glucosamine (PNAG vaccine). Through this collaboration, the companies will co-develop and commercialise in India and other low income and lower middle-income countries.

18th September, 2024: Pfizer has launched 'the Analytics Gateway', the first dedicated commercial analytics centre in Mumbai,. This centre will support Pfizer's international non-US markets by providing data and analytics insights to benefit patients.

30th September, 2024: Central Drug Research Institute (CDRI), Lucknow and Zydus Lifesciences, Ahmedabad have entered into joint agreement to pursue preclinical studies for treating chronic kidney disease (CKD) induced osteoporosis as well as postmenopausal osteoporosis. Data from antibody-based therapies implicate the role of protein Sclerostin in the dysregulation of bone metabolism evident from high levels of Sclerostin in patients with advanced stages of CKD and osteoporosis. Under this agreement, efforts will be undertaken to discover small molecule inhibitors of protein and to develop its oral medication for commercialization.

11th October, 2024: Based on the comprehensive review of the product dossier consisting of non-clinical, US/EU Phase 1, Global Phase 2 and India Phase 3 clinical studies conducted over the last 15 years, the Subject Expert Committee (SEC) of the Central Drugs Standard Control Organisation (CDSCO) accorded a favourable recommendation for Miqnaf (nafithromycin). Miqnaf is a novel antibiotic developed by Wockhardt for the treatment of community-acquired bacterial pneumonia (CABP) in adults. This final recommendation would pave the way for gaining DCGI's final approval for Miqnaf.

14th October, 2024: Under Paragraph 19 of the Drugs Prices Control Order due to increasing input costs and the threat of some manufacturers discontinuing supplies, the National Pharmaceutical Pricing Authority (NPPA) has increased the ceiling price of 11 scheduled formulations by 50% which are used as first-line treatment for various conditions including asthma, glaucoma, thalassemia, tuberculosis and mental health disorders.

24th October, 2024: The National Pharmaceutical Pricing Authority (NPPA) has issued an office memorandum directing the concerned manufacturers to reduce the MRP on three anti-cancer drugs, Trastuzumab, Osimertinib and Durvalumab.

25th October, 2024: Zydus Lifesciences has received in principle acceptability from World Health Organisation (WHO) for it is indigenously developed and manufactured typhoid conjugate vaccine, ZyVac® TCV. The vaccine is indicated for active immunisation against Salmonella typhi infection in the age group of 6 months to 65 years. By this prequalification, ZyVac® TCV manufactured at Zydus Biotech Park, Ahmedabad will be eligible for procurement programme by United Nations (UN) agencies.

05th November, 2024: The National Pharmaceutical Regulatory Agency of Malaysia granted good manufacturing practices (GMP) approval to robotic pre-filled syringe facility at Baddi unit Venus Remedies making it the first Pharmaceutical Inspection Co-operation Scheme (PIC/S) accreditation for Venus Remedies' pre-filled syringe (PFS) facility.

Source:
https://economictimes.indiatimes.com/
www.expresspharma.in

APTI Forum News

1. Dr. Neelima Dhingra received the National Award “Sarvshreth Divyanjan” 2022

President Droupadi Murmur conferred the National Award “Sarvshreth Divyanjan” 2022 on December 3, 2022 to Dr. Neelima Dhingra, UIPS, Panjab University, Chandigarh for individual excellence award in the female category, by the Ministry of Social Justice and Empowerment, under the Department of Empowerment of Persons with Disabilities for outstanding achievements in the field of education, research & extra co-curricular contributions. Dr. Neelima Dhingra has been granted with Indian patent (patent number: 535328) on April 26, 2024 on Lantadene ethers of formula (i) process for their preparation and a pharmaceutical composition thereof.

2. Ms. Punam Gaba secured the first prize in an oral paper presentation

Ms. Punam Gaba, a faculty member at Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, BELA, has secured the first prize in an Oral Paper Presentation at Minerva College of Pharmacy, Indora (HP). Her outstanding research and presentation skills were recognized at the event. Dr. Shailesh Sharma, Director of the college, congratulated Ms. Gaba for her hard work and dedication to research.

3. Ms. Dipti Atul Bonde received Gold and Silver Medals in NPTEL courses

Ms. Dipti Atul Bonde, Assistant Professor at P. R. Pote Patil College of Pharmacy, Amravati have received Gold and Silver Medals in NPTEL courses for patent drafting for beginners and research methodology respectively.

4. Prof. (Dr.) Shailesh Sharma honoured with ISTE best teacher award 2024

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, BELA's Director, Prof. (Dr.) Shailesh Sharma, received the ISTE Best Teacher Award 2024. The award was presented at the Indian Society for Technical Education (ISTE) Faculty Convention 2024, held at Bhai Gurdas Institute of Engineering and Technology, Sangrur. Hon'ble Vice Chancellor of IKG Punjab Technical University, Jalandhar, Dr. Sushil Mittal, Former Hon'ble Vice Chancellor of MRSPTU Dr. Buta Singh and ISTE president and members bestowed the award upon Dr. Sharma. This recognition acknowledges Dr. Sharma's tireless efforts, dedication, and outstanding achievements in education and research, as well as his exceptional teaching and learning experience.

5. Dr. B. Anupama honoured with the Best Teacher Award

Dr. B. Anupama, M.Pharm, PhD, Associate Professor and HOD, Department of Pharmaceutical Chemistry, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh has been honoured with the “Best Teacher Award” from council for skills and competencies on October 5, 2024 on International teachers day.

6. Mrs. S. Triveni best woman coordinator award by JNTUA

Mrs. Triveni was honored with the Best Woman Coordinator Award by Jawaharlal Nehru Technological University Anantapur (JNTUA) on the occasion of Teachers' Day 2024. This award recognizes her exemplary dedication to empowering women in academia and her impactful initiatives for student and faculty development. Her leadership in women empowerment cell (WEC) has led to numerous events aimed at professional growth, skill development, and community service.

7. Ms. Vaishali Raghuwanshi, Assistant Professor (Pharmaceutics) of Sri Aurobindo Institute of Pharmacy, Indore

Awarded research fellowship for the training of young scientists in (MPCST), Bhopal 2023 for actively participating in oral presentation sponsored by MPCST 38th M.P. Young Scientist Congress held on 17-19 March, 2023. Published Indian Patent (application number: 202321042912A) on Orodispersible Tablet of Memantine Hydrochloride and Preparation Thereof.


M.P. Council of Science and Technology
Vigyan Bhawan, Nehru Nagar, Bhopal - 462003
Hosted by
Samrat Ashok Technological Institute
Civil Lines, Vidisha - 464001
38th M.P. Young Scientist Congress
March 17 - 19, 2023
This is to certify that
VAISHALI RAGHUWANSHI
of
SRI AUROBINDO INSTITUTE OF PHARMACY, INDORE
has presented his/her research paper in the discipline of
Pharmaceutical Sciences
at the 38th M.P. Young Scientist Congress organized by
Samrat Ashok Technological Institute, Vidisha
during March 17 - 19, 2023.
He/she awarded Fellowship for Training of Young Scientists
of M.P. Council of Science and Technology.
Prof. R.K. Pandit
Director, SATI, Vidisha
Dr. Anil Kothari
Director General, MPCST, Bhopal

8. Ph.D. degree awarded to Ms. Priyatama Powar

Ms. Priyatama Powar has been awarded her doctorate for exceptional research on the “Development of Novel Phytoformulation Using Endophytic Fungi,” in July 2024 from Savitribai Phule Pune University, Pune. Her research was conducted under the expert guidance of Dr. Shilpa Chaudhari. Dr. D.Y. Patil College of Pharmacy, Akurdi, Pune, under the leadership of the Principal Dr. N.S. Vyawahare. She has presented her findings at both National and international conferences, patents providing valuable insights and direction for further exploration in this critical area of healthcare.

9. Ph.D. degree awarded to Ms. Sarika Nikam

Ms. Sarika Nikam, Assistant professor, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune has been awarded a Ph.D. degree in September 2023 from Savitribai Phule Pune University, Pune. Her thesis, titled “Development and Evaluation of Nanoparticulate Formulation for Drug Delivery to Skin,” was completed under the supervision of Dr. Shilpa Chaudhari. The research was conducted at the Dr. D.Y. Patil College of Pharmacy, Akurdi, Pune, a recognized research center under the leadership of the Principal Dr. N.S. Vyawahare.

10. PhD Awarded to Baljeet Singh

Dr. Baljeet Singh, Pharmacy Officer, Govt. Of Punjab obtained his Ph.D. from I.K.G. Punjab Technical University, Kapurthala in Punjab. His thesis title was " Design and Synthesis and anticancer activity of novel quinazolin 4(3H)- One Derivatives " under the guidance of Dr. Shailesh Sharma, Director and Professor of Pharmacy at Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial (Autonomous) College of Pharmacy, Bela, Ropar. He published 03 research papers. He also received the Best Presentation Award for their research work.

11. World Pharmacist Day 2024 Celebrations at Mother Terasa College of Pharmacy, Illuppur

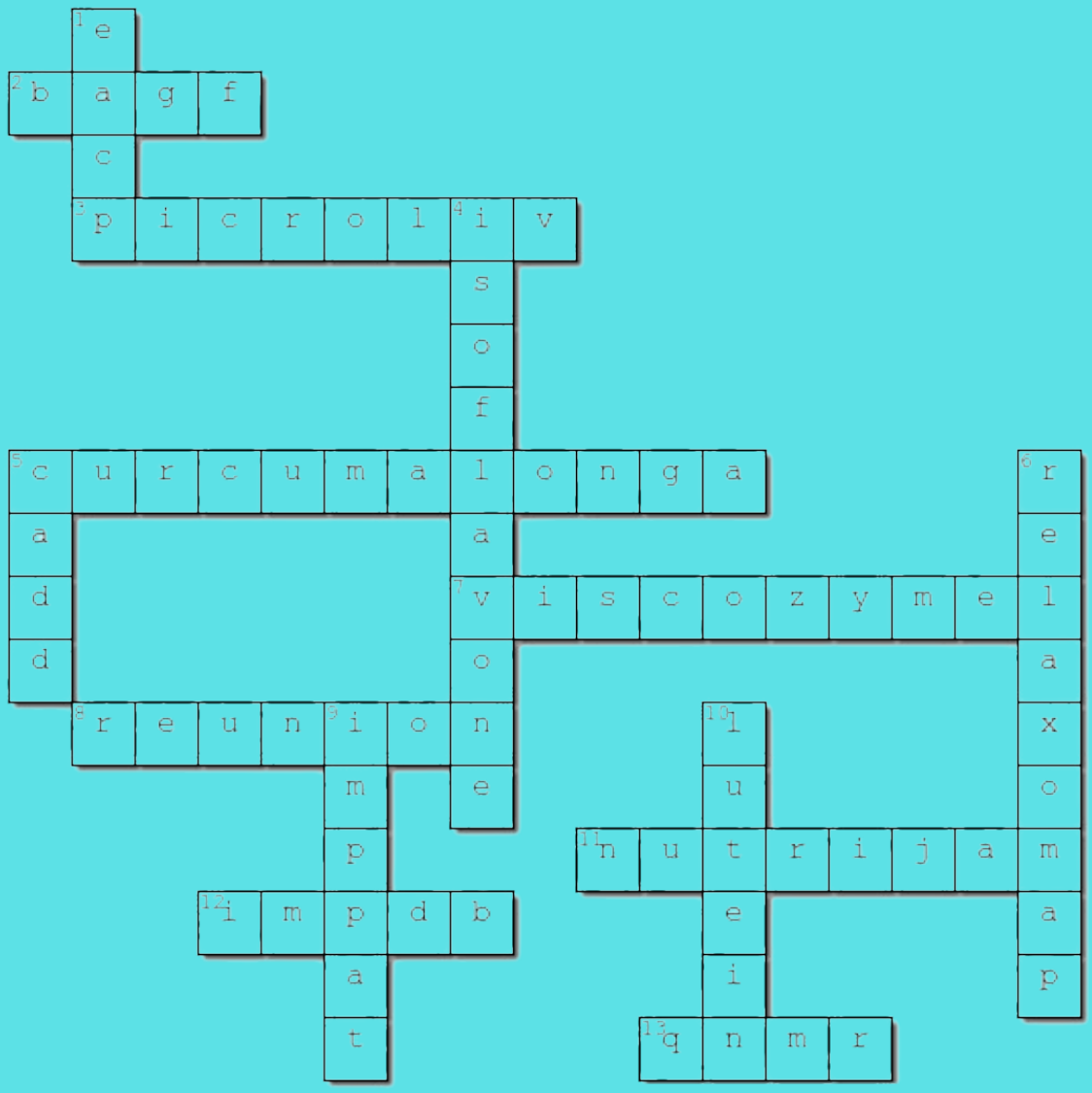
Mother Terasa College of Pharmacy, Illuppur, Pudukkottai, TamilNadu celebrated World Pharmacist Day on September 25, 2024. The event was highlighted by the presence of Dr. Balakumar Pitchai, Professor, Director, Research Training, Publications, Office of Research & Development, Periyar Maniammai Institute of Science and Technology (Deemed to be University), Thanjavur, as the esteemed Chief Guest. The celebration was further graced by the presence of Mr. R. C. Uthaya Kumar, Chairman of the Mother Terasa Group of Institutions, and the event commenced with a warm welcome speech by Prof. Dr. T. Shri Vijaya Kirubha, Principal of the college, who highlighted the significance of World Pharmacist Day in recognizing and honouring the contributions of pharmacists to the healthcare field. Poster presentations, essay writing, and sports competitions were organised. The winners were honoured with prizes in a special award ceremony, adding to the spirit of celebration. The programme concluded with a vote of thanks delivered by Mrs. A. Gayathri, Assistant Professor. The World Pharmacist Day celebrations at Mother Terasa College of Pharmacy raised awareness about the critical role of pharmacists and fostered a sense of responsibility and professionalism among future pharmacists.

11. World Pharmacist Day celebrated at BELA Pharmacy College

World Pharmacist Day was celebrated on September 25, 2024, at Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela (Ropar) (Autonomous). The event kicked off with a rally led by the college's director, Dr. Shailesh Sharma, along with Dr. Ajay Singh Kushwaha and Dr. Suman Lata. The rally started from the college to village Bela before returning to campus. During the opening of the program, Dr. Sharma highlighted the significance of the day, noting that it marks the anniversary of the International Federation of Pharmacists, which was established in 2012.

Name: _____

Complete the crossword puzzle below



Across

2. Bioactivity-guided fractionation abbreviated (**bagf**)
3. CSIR-CDRI phytopharmaceutical for NAFLD (**picroliv**)
5. Monograph of Phytopharmaceutical ingredient in IP-2022 (**curcumalonga**)
7. Multi-enzyme complex used for extraction (**viscozymel**)
8. Commercialized CSIR-CDRI Plant Extract A-4744 (**reunion**)
11. Patented herbal invention of CSIR-National Botanical Research Institute (NBRI) (**nutrijam**)
12. Indian Medicinal Phytochemical Database Curated for Drug Designing (**impdb**)
13. Methodology to assay phytomarkers (**qnmr**)

Down

1. Enzyme-assisted cold pressing abbreviated (**eacp**)
4. Phenolic phytonutrient (**isoflavone**)
5. Technique used for Combinatorial Drug Discovery (**cadd**)
6. Commercialized aromatherapy based herbal oil developed by CSIR-CIMAP (**relaxomap**)
9. Manually curated database of Indian Medicinal Plants, Phytochemistry And Therapeutics (**imppat**)
10. Xanthophyll with anticancer properties (**lutein**)

Name: _____

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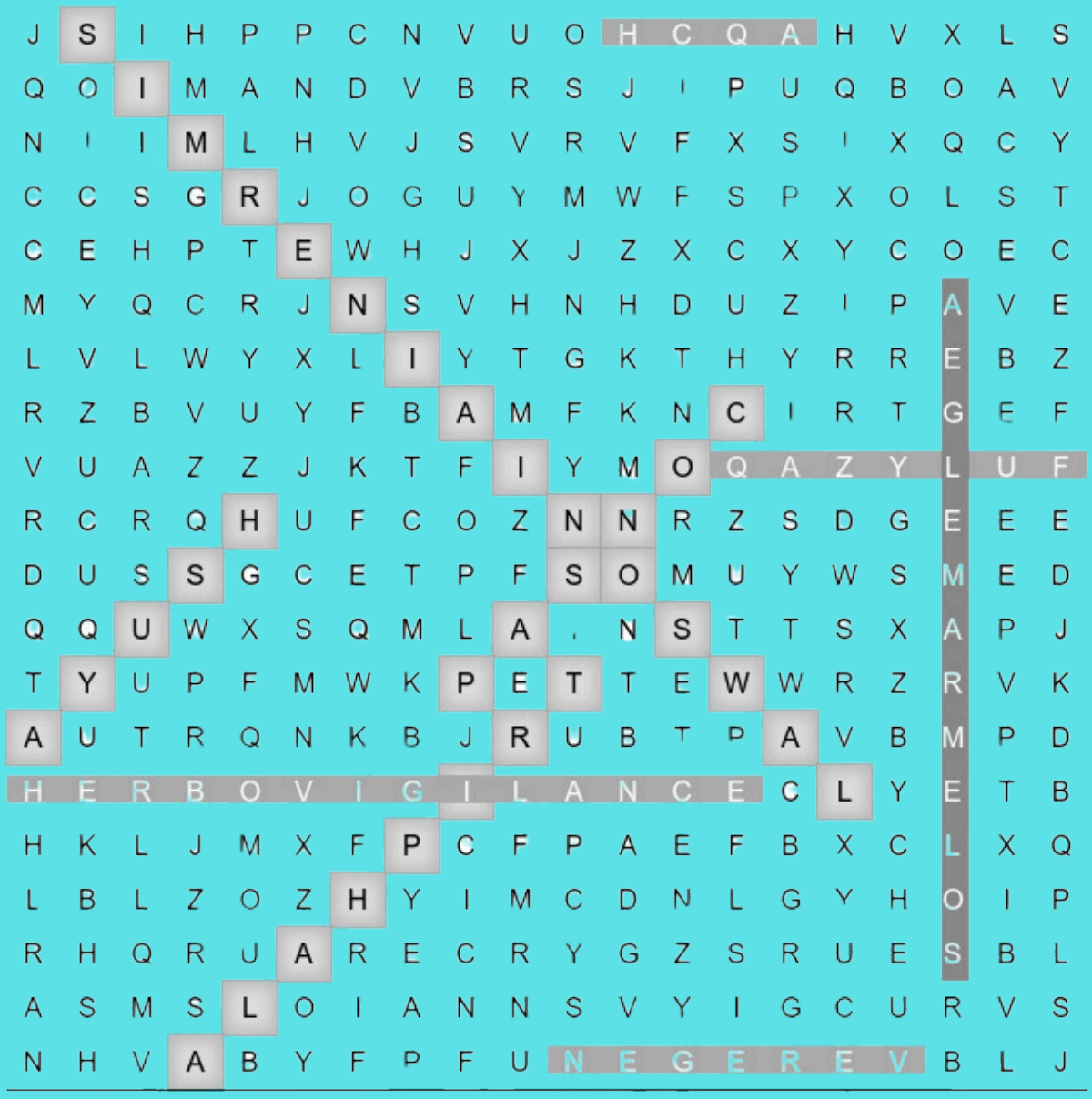

AYUSH
FULYZAQ
LAWSONIAINERMIS
TRIPHALA
AQCH
HERBOVIGILANCE
VEREGEN
AEGLEMARMELOS
CONSAP

WORD SCRAMBLE

Solution
KNAPSACK
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LOTUS LOGO STORY

As a lotus is able to emerge from muddy waters un-spoilt and pure it is considered to represent a wise and spiritually enlightened quality in a person; it is representative of a woman who carries out her tasks with little concern for any reward and with a full liberation from attachment. Lotus-woman in the modern sense of women's qualities: she is superbly intelligent, highly educated, and totally committed to individualism. She is politically astute and works incessantly for a better and more humane society. She is exquisite in her taste for music, art and culture, abounds in social graces and performs brilliantly in communication.