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).

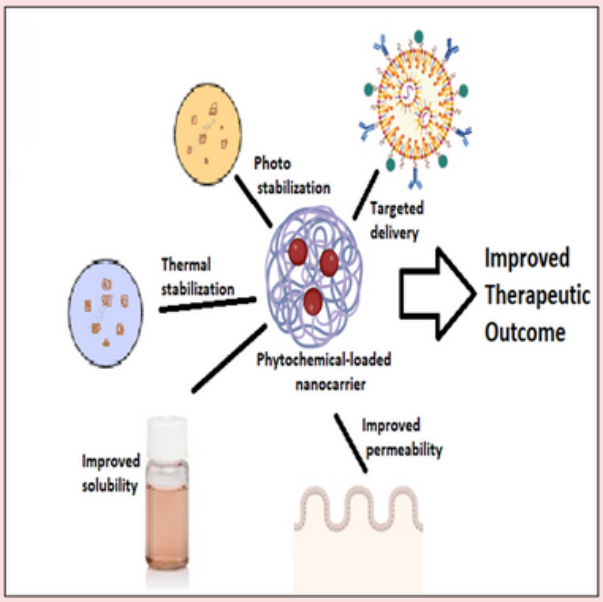

Figure 1. Functions of nanocarriers to improve therapeutic outcomes of phytopharmaceuticals

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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