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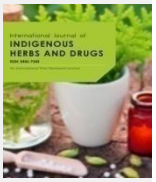

NANOTECHNOLOGY BASED PHYTOPHARMACEUTICALS

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Abstract

Nanotechnology-based phytopharmaceuticals represent a cutting-edge advancement that bridges traditional herbal medicine with modern nanoscience to enhance therapeutic efficacy, safety, and patient compliance. The inherent limitations of phytoconstituents-such as poor solubility, low bioavailability, instability, and rapid metabolism-have long restricted their clinical potential. Nanotechnology enables the design of nanosized carriers, including polymeric nanoparticles, liposomes, phytosomes, nanoemulsions, solid lipid nanoparticles, dendrimers, and nanocrystals, which encapsulate, protect, and deliver plant-derived bioactives in a controlled and targeted manner. These delivery systems improve solubility, protect against enzymatic degradation, enhance permeability across biological membranes, and allow sustained drug release. Significant therapeutic applications have been reported in oncology, neurodegenerative disorders, cardiovascular protection, antimicrobial therapy, wound healing, and hepatoprotection. Despite these remarkable advantages, challenges such as large-scale production, formulation stability, toxicity assessment, and regulatory validation continue to hinder clinical translation. Thus, nanotechnology-based phytopharmaceuticals signify a paradigm shift in drug delivery science, integrating traditional plant-based medicine with precision nanotechnology to develop safer, more effective, and environmentally friendly therapies.

Keywords: Herbal nanocarriers, Nano emulsions, Liposomes, Phytosomes, Targeted drug delivery, Phytochemical stability.

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Introduction

The integration of nanotechnology into phytopharmaceuticals has catalyzed a paradigm shift in the field of herbal medicine, offering solutions to major formulation and therapeutic challenge. Plant-derived medicines often feature poor water solubility, susceptibility to degradation, and low absorption, resulting in variable clinical outcomes in conventional use. Nanotechnology-enabled delivery systems enhance these medicines' bioavailability, stability, and efficacy by protecting active compounds and enabling controlled release at targeted sites. Phytopharmaceuticals, commonly referred to as plant-derived medicines, have been used for centuries in traditional systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani. Despite their proven therapeutic value, a major drawback of herbal drugs lies in their poor solubility, low bioavailability, and instability in physiological conditions. For example, compounds like curcumin and quercetin exhibit strong antioxidant and anticancer properties but fail to reach therapeutic plasma levels when administered orally due to rapid metabolism and degradation.

The Integration of nanotechnology into phytopharmaceuticals has transformed this scenario. Nanotechnology enables the design of nanosized carriers (1–100 nm) that can encapsulate, protect, and deliver phytoconstituents directly to the desired site of action. These nano-based formulations not only improve absorption, stability, and pharmacokinetics but also allow controlled release and targeted delivery, thereby enhancing therapeutic outcomes while minimizing side effects.

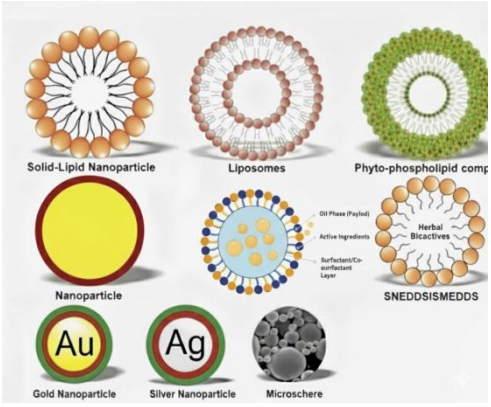

Fig 01: Nanotechnology Based Phytopharmaceuticals

Types of Nano-Delivery Systems in Phytopharmaceuticals

A variety of nano carriers [Table 1] are employed to deliver phytochemicals, each with unique advantages Fig 01 [1].

Nanoparticles (Polymeric nanoparticles: PLGA, chitosan, PEG-based)

One of the most promising and extensively studied systems within this field is polymeric nanoparticles. These nanosized carriers, typically within the range of 10–400 nanometers, are constructed using biocompatible and biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG). They offer improved solubility, stability, and bioavailability of phytoconstituents-plant-derived bioactive compounds that are often poorly soluble or unstable in biological environments [1].

The core objective of polymeric nanoparticle systems in phytopharmaceuticals is to enhance the delivery of natural medicinal compounds by addressing limitations such as poor absorption, low membrane permeability, enzymatic degradation, and rapid systemic clearance. These nanoparticles enable controlled and targeted drug release, reduce dosing frequency, and minimize toxicity, making them powerful tools in delivering herbal therapeutics. The versatility of PLGA, chitosan, and PEG polymers allows researchers to tailor the nanoparticles for specific diseases, tissues, or delivery routes, rendering them a cornerstone in the development of next-generation phytopharmaceuticals [1].

Mechanism of Action

The mechanism of action of polymeric nanoparticles revolves around their unique ability to encapsulate, protect, and release phytochemicals in a controlled and targeted manner. Depending on the formulation, polymeric nanoparticles can exist as nanospheres or nanocapsules. Nanospheres are matrix-type systems where the drug is uniformly distributed throughout the polymer. Nanocapsules consist of a reservoir-like structure with an inner core containing the drug and an outer polymer shell controlling its release. Once administered, these nanoparticles interact with biological fluids and tissues to deliver the encapsulated phytochemicals to their target sites through diffusion, erosion, or polymer degradation mechanisms [1].

PLGA Nanoparticles

PLGA (Poly Lactic-co-Glycolic Acid) is a synthetic, biodegradable copolymer approved by the U.S. FDA and EMA for controlled drug delivery. It hydrolyzes into non-toxic monomers, lactic acid, and glycolic acid, which are naturally metabolized in the body. In phytopharmaceutical formulations, PLGA nanoparticles encapsulate both hydrophilic and lipophilic plant compounds and degrade slowly, ensuring sustained release [2].

Chitosan Nanoparticles

Chitosan is a natural polysaccharide derived from chitin found in crustacean shells. It exhibits unique mucoadhesive, biocompatible, and biodegradable properties. Its slightly positive charge allows strong electrostatic interaction with negatively charged mucosal surfaces, improving absorption of phytochemicals through biological membranes such as the gastrointestinal or nasal epithelium. Chitosan nanoparticles are particularly useful for the delivery of hydrophilic plant compounds and have shown great promise in oral, nasal, ocular, and dermal applications [3].

PEG-Based Nanoparticles

Polyethylene glycol (PEG) is widely recognized for its "stealth" properties due to its hydrophilic nature and ability to evade immune detection. PEGylation, the process of coating nanoparticles with PEG chains, provides steric stabilization and prevents opsonization by serum proteins, thereby prolonging circulation time in the bloodstream. PEG-based nanoparticles can be formed independently or in combination with other polymers such as PLGA and chitosan. PEGylation also improves water solubility, reduces aggregation, and enhances the bioavailability of encapsulated phytochemicals, particularly for chronic therapies and cancer treatments [3].

Through these intricate mechanisms, polymeric nanoparticles not only sustain the release of phytoconstituents but also enable targeted delivery, crossing barriers such as the intestinal epithelium or even the blood–brain barrier (BBB), which is critical for neurological and systemic therapies [3].

Advantages of Polymeric Nanoparticles

Enhanced Bioavailability: They improve the solubility and dissolution of poorly soluble phytochemicals, significantly enhancing their absorption and systemic availability.

Controlled and Sustained Release: Nanoparticle formulations regulate the release of bioactives over time, maintaining optimal therapeutic concentrations and reducing dosing frequency.

Targeted Drug Delivery: Surface modification with ligands, antibodies, or PEG allows nanoparticles to specifically target diseased tissues or cells, reducing off-target effects and systemic toxicity.

Improved Stability and Protection: Encapsulation protects phytoconstituents from degradation caused by light, pH changes, or enzymatic activity, ensuring prolonged shelf life and bioactivity [4].

Therapeutic Applications

Polymeric nanoparticles have become a cornerstone in the development of nanoscale phytopharmaceuticals due to their extensive therapeutic potential across multiple disease domains.

Cancer Therapy: Many phytochemicals such as curcumin,

resveratrol, quercetin, and paclitaxel exhibit potent anticancer properties but suffer from poor solubility and bioavailability. Formulation within PLGA or chitosan nanoparticles enhances their uptake by cancer cells through endocytosis and provides controlled release, resulting in improved cytotoxic efficacy.

Neurodegenerative Diseases: Phytochemicals such as ginsenosides, bacosides, berberine, and quercetin have shown neuroprotective effects but face challenges in crossing the BBB. PEG- and chitosan-based nanoparticles have the ability to overcome this barrier, enhancing their cerebral bioavailability.

Cardiovascular and Anti-Inflammatory Therapy

Polymeric nanoparticles have been used to deliver natural antioxidants and anti-inflammatory agents like baicalin, silymarin, and EGCG. Silymarin-loaded PLGA nanoparticles, for instance, show improved hepatoprotective and antioxidant effects, offering enhanced therapeutic efficacy in liver and heart diseases.Antimicrobial and Wound Healing Applications: Chitosan nanoparticles, known for their inherent antimicrobial properties, have been used to deliver phytochemicals such as allicin, curcumin, and aloe vera extracts [4].

Antidiabetic and Antioxidant Applications: Plant-derived compounds like gymnemic acids, catechins, and gallic acid have demonstrated improved bioefficacy when formulated into polymeric nanoparticles [4].

Limitations of Polymeric Nanoparticles

High Production Cost: Manufacturing polymeric nanoparticles involves energy-intensive and expensive techniques.

Scale-Up Difficulties: Ensuring uniform particle size, homogeneity, encapsulation efficiency, and reproducibility during large-scale production is complex.

Storage and Stability Issues: Nanoparticles may undergo aggregation, sedimentation, or drug leakage during prolonged storage.

Toxicity and Safety Concerns: Although PLGA, chitosan, and PEG are biocompatible, certain degradation intermediates or polymer residues may induce cytotoxic effects.

Regulatory Challenges: The regulatory framework for nanotechnology-based herbal products is still evolving [4].

Liposomes and Phytosomes

In phytopharmaceuticals, nanotechnology-based delivery systems have paved the way for the efficient use of herbal and plant-derived compounds that often suffer from poor solubility, instability, low permeability, and limited bioavailability. Among the most promising vesicular systems designed for plant-based therapeutics are liposomes and phytosomes. These systems have demonstrated the ability to overcome many limitations associated with conventional herbal formulations by improving solubility, protecting sensitive compounds from degradation, enhancing absorption, and ensuring targeted delivery [5].

Liposomes are spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core. This structural organization makes them versatile carriers for both hydrophilic and lipophilic phytoconstituents. Both of these systems represent significant advancements in nanotechnology-based phytopharmaceuticals, allowing herbal drugs to achieve efficacy levels comparable to synthetic medicines [5].

Mechanism of Action

The function and mechanism of liposomes and phytosomes in phytopharmaceuticals depend on their unique structural configurations and how they interact with biological membranes and fluids.

Liposomes

Liposomes are vesicular structures formed by amphiphilic phospholipids in an aqueous environment, organizing into spherical bilayers. Hydrophilic drugs can be enclosed in the aqueous core, while lipophilic drugs are embedded within the lipid bilayer. This configuration allows the simultaneous encapsulation of both types of molecules, providing versatility in formulation. When administered, liposomes improve the delivery of phytoconstituents by:

Protecting sensitive compounds: Encapsulation shields phytochemicals from enzymatic, oxidative, or hydrolytic degradation in the gastrointestinal tract.

Prolonging circulation: Liposomes can be modified with hydrophilic polymers like polyethylene glycol (PEG), preventing rapid clearance by the mononuclear phagocyte system, thus increasing systemic retention.

Enhancing absorption and targeting: Liposomes merge or interact with biological membranes due to their phospholipid composition, facilitating the direct transfer of encapsulated compounds into cells. Targeted delivery can be further achieved through ligand conjugation for receptor-mediated uptake in diseased tissues, especially in cancer therapy [5].

Controlled release

The rate of release depends on lipid composition, particle size, and surface properties, allowing for sustained and site-specific drug delivery.

Phytosomes

Phytosomes (phyto-lipid complexes) differ from liposomes in their mechanism of formulation and interaction with biological membranes. In phytosomes, phytoconstituents form molecular complexes with phospholipids—typically phosphatidylcholine-through hydrogen bonding between the polar functional groups of the phytochemical and the polar head of the phospholipid. This intimate bonding transforms poorly soluble plant compounds into amphiphilic lipid-compatible molecules capable of easily penetrating lipid-rich biological membranes.

Once administered, phytosomes enhance the absorption and bioavailability of phytoconstituents in the following ways: The lipid portion improves solubility in the gastrointestinal environment. The complex improves membrane fluidity and facilitates direct uptake into enterocytes. The phytolipid complex protects the phytochemical from premature degradation and inactivation [6].

Advantages of Liposomes and Phytosomes

Enhanced Solubility and Bioavailability: Many phytochemicals such as curcumin, quercetin, and silymarin have poor solubility in water, leading to limited absorption. Liposomes and phytosomes significantly improve solubility

and enhance their bioavailability by integrating them into biocompatible lipid systems.

Protection from Degradation: Both systems protect active phytochemicals from enzymatic, oxidative, and hydrolytic degradation during storage and after administration, preserving their potency.

Controlled and Sustained Release: Liposomes can be engineered to release their payload gradually, ensuring long-term therapeutic effects, reducing dosing frequency, and minimizing systemic side effects.

Biocompatibility and Low Toxicity: The phospholipids used in these systems are similar to biological membranes, rendering them highly biocompatible, biodegradable, and safe for human use.

Dual Solubility: Liposomes encapsulate both hydrophilic (in aqueous core) and lipophilic (in lipid bilayer) compounds, offering flexibility for various phytochemicals [6].

Therapeutic Applications

Cancer Therapy

Phytoconstituents like curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) display strong anticancer effects but suffer from limited solubility and stability. Liposomal encapsulation overcomes these issues by enhancing compound retention and targeting tumor sites. PEGylated liposomes further improve circulation time and tumor targeting through the Enhanced Permeability and Retention (EPR) effect.

Neuroprotective Applications

Natural compounds such as ginkgo flavonoids, berberine, and ginsenosides play key roles in neuroprotection. Liposomal systems can deliver these phytoconstituents to the brain, improving their concentration and activity in the central nervous system.

Cardiovascular and Hepatoprotective Applications

Silymarin phytosomes, derived from milk thistle extract, have shown almost double the systemic bioavailability compared to unmodified silymarin, protecting hepatocytes against oxidative and drug-induced damage.

Anti-inflammatory and Antioxidant Applications

Liposomes and phytosomes deliver phytochemicals such as curcumin, quercetin, and boswellic acids for managing chronic inflammatory diseases [7].

Dermatological and Cosmetic Applications

Due to their ability to penetrate skin layers effectively, liposomes and phytosomes are used in topical formulations for skin protection, moisturization, and anti-aging therapies [7].

Limitations

Scale-Up Challenges: Large-scale manufacturing of liposomes and phytosomes with consistent particle size and encapsulation efficiency is technically demanding.

Storage and Stability Issues: Liposomes are sensitive to temperature, pH, and oxidation, causing aggregation or drug degradation during storage.

High Production Cost: Sophisticated equipment and quality control significantly increase costs.

Limited Clinical Validation: Large-scale, long-term human studies are limited, and regulatory pathways are still under development [7].

Nanoemulsion based Phytopharmaceuticals

Nanoemulsion-based phytopharmaceuticals represent a remarkable advancement in herbal medicine delivery, offering greatly enhanced solubility, stability, bioavailability, and therapeutic efficacy compared to conventional botanical preparations. These systems use nanoscale emulsions to encapsulate bioactive compounds from plant sources, thereby addressing long-standing formulation and clinical challenges.

Phytopharmaceuticals-bioactive ingredients derived from plants-suffer from limitations such as poor water solubility, instability, and unpredictable absorption, which hinder therapeutic outcomes. The application of nanoemulsion technology has emerged as a transformative strategy for addressing these issues. Nanoemulsions are colloidal dispersions characterized by droplet sizes ranging from 20-200 nm, stabilized by surfactants and co-surfactants [8].

Mechanism and Formulation

Nanoemulsions create a substantial increase in surface area, enabling better solubilization and transport of both hydrophilic and lipophilic phytoconstituents. By encapsulating these plant actives within the oil or aqueous droplets, nanoemulsions protect them from enzymatic degradation, pH shifts, and oxidation, allowing for more controlled and efficient delivery. Common preparation methods include high-pressure homogenization, ultrasonication, and spontaneous emulsification, with the choice of oils and surfactants tailored to the phytochemical's properties [8].

Advantages

Solubility & Bioavailability: Nanosized droplets dramatically increase solubility and the absorption of poorly water-soluble phytochemicals. This leads to higher plasma concentrations and improved efficacy for drugs and supplements.

Targeted & Sustained Release: Surface modification of nanoemulsions can enable site-specific delivery (e.g., tumor targeting), controlled release, and minimally fluctuating plasma levels.

Protection of Actives: Encapsulation helps avoid loss of activity due to physical or chemical instability, such as hydrolysis or oxidation.

Formulation Versatility: Nanoemulsions can be formulated as gels, creams, foams, liquids, or sprays, and administered orally, topically, intravenously, among other routes.

Improved Patient Compliance: Taste masking, ease of administration, and reduction of dose-related side effects contribute to better treatment adherence [9].

Therapeutic and Industrial Applications

Nanoemulsion-based phytopharmaceuticals have been successfully researched for

Oral and Parenteral Delivery: For antioxidant, anti-inflammatory, antimicrobial, and anticancer phytodrugs (e.g., cinnamon oil-based azithromycin nanoemulsion, resveratrol, essential oil formulations).

Topical and Transdermal Delivery: Effective in skin disorders, wound healing, and cosmetic preparations due to

excellent permeability and depot formation in skin layers.

Food and Nutraceutical Sector: Used for encapsulating vitamins, nutraceuticals, preservatives, and flavoring agents to increase bio efficacy and shelf-life.

Specialized Applications: Ocular, pulmonary, and brain-targeted delivery have been explored, taking advantage of nanoemulsion's ultra-small droplet size [9].

Limitations and Challenges

Despite their benefits, nanoemulsion-based phytopharmaceuticals face technical limitations such as

Physical Instability: Susceptibility to Ostwald ripening, phase separation, and coalescence during storage or transportation.

High Surfactant Demand: Formulation often requires significant surfactant concentrations, raising concerns about toxicity and regulatory approval.

Scalability: Transition from laboratory to industrial scale demands precise control over processing parameters and batch reproducibility.

Regulation and Safety: Adequate evaluation of nanoemulsion toxicology and regulatory frameworks for phytopharmaceuticals are still evolving [9].

Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles are submicron colloidal carriers typically ranging from 50 to 1000 nm composed of lipids that are solid at room and body temperature. These particles are stabilized by surfactants or emulsifiers, forming stable nanoparticles with a solid lipid core capable of encapsulating lipophilic and some hydrophilic compounds. As the first generation of lipid-based nanocarriers, SLNs combine the advantages of traditional carriers like emulsions and liposomes with improved physical stability, biocompatibility, and easier scale-up for industrial production [10].

The lipid matrix of SLNs is formulated using physiological lipids such as triglycerides, glycerides, fatty acids, waxes, and sterols, which degrade into non-toxic metabolites, thus ensuring excellent biocompatibility and safety for human use. SLNs have emerged as a promising delivery system in phytopharmaceuticals due to their ability to enhance the solubility, stability, and biological efficacy of natural compounds. Additionally, they allow for controlled release and targeted delivery, which is highly desired for chronic diseases and neurological disorders. The diversity of lipid choices and surfactants enables tailoring SLNs for different routes of administration including oral, topical, parenteral, and pulmonary delivery [10].

Mechanism of Action

The mechanism by which SLNs improve phytopharmaceutical delivery is centered on their solid lipid core matrix. This core encapsulates the active plant compound either by dissolving it within the lipid or dispersing it homogeneously throughout the matrix. The solid state of the lipid limits molecular mobility, thereby protecting the encapsulated compound from premature degradation caused by enzymatic activity or oxidation in biological environments [10].

Upon administration, SLNs offer several mechanistic benefits

Protection from Degradation: The solid lipid core shields the phytoconstituent from harsh physiological conditions such as gastric acids and metabolic enzymes, enhancing their intact passage to systemic circulation.

Controlled and Sustained Release: Due to the solid nature of the core, diffusion of the drug is slow and sustained over time, which helps in maintaining therapeutic plasma concentrations over extended durations and reduces the need for frequent dosing.

Enhanced Absorption: SLNs improve the solubility and dissolution rate of lipophilic phytochemicals, which are otherwise poorly absorbed in the gastrointestinal tract. The small particle size facilitates uptake through intestinal mucosa, sometimes via lymphatic absorption, bypassing first-pass metabolism.

Targeted Delivery: SLNs can be surface-modified with ligands or antibodies, enabling targeted binding to specific cells or tissues such as tumors or inflamed areas, improving localization while minimizing systemic toxicity.

Improved Penetration: For topical applications, SLNs enhance skin penetration by disrupting the stratum corneum lipid packing or via follicular delivery, substantially increasing drug bioavailability in dermal layers [10].

Advantages of Solid Lipid Nanoparticles (SLNs)

High Physical and Chemical Stability: The solid lipid matrix provides better drug retention, reduced leakage, and increased long-term stability.

Biocompatibility and Biodegradability: Composed of physiological lipids, SLNs are highly biocompatible and biodegradable.

Controlled Drug Release: SLNs enable sustained and controlled drug release, improving therapeutic efficacy and patient compliance.

Improved Bioavailability: SLNs increase the solubility and absorption of poorly water-soluble phytoconstituents.

Versatile Administration Routes: SLNs can be formulated for oral, topical, injectable, ocular, pulmonary, and nasal delivery [10]

Therapeutic Applications

Anticancer: SLNs improve delivery of phytochemicals like curcumin to tumor cells, enhancing cytotoxicity and apoptosis.

Neuroprotective Applications: SLNs facilitate the delivery of compounds such as resveratrol across the blood–brain barrier.

Anti-inflammatory and Antioxidant Delivery: SLNs deliver phytochemicals like quercetin and EGCG with improved stability and sustained release, aiding in cardiovascular and metabolic disorders.

Topical and Cosmeceutical Uses: SLNs enhance dermal penetration and film formation on the skin, useful in UV protection, anti-aging, and skin repair formulations [10]

Limitations and Challenges

Drug Loading Capacity: The crystalline structure limits drug encapsulation.

Polymorphic Transitions: Storage-induced lipid rearrangements can cause drug expulsion.
Burst Release Effect: Initial burst may cause high drug concentration.
Particle Aggregation: Improper stabilization can lead to aggregation.
Limited Encapsulation of Hydrophilic Drugs: Hydrophilic compounds are challenging to retain in SLNs [10].

Dendrimers, Nanocrystals, and Nanofibers

Nanotechnology has opened new horizons in the delivery of phytochemicals, transforming traditional herbal medicine into sophisticated, targeted, and efficient therapeutic systems. Among various nanoscale carriers, dendrimers, nanocrystals, and nanofibers stand out due to their unique structural advantages and functionalities. These systems enhance drug solubility, stability, bioavailability, and targeted delivery, overcoming intrinsic limitations of many herbal compounds such as poor water solubility, low permeability, and rapid degradation.

Dendrimers are highly branched, monodisperse, nanosized molecules with a tree-like architecture [11,13]. They consist of a central core, repetitive branching units (generations), and multiple surface functional groups. Thanks to their multivalency, dendrimers provide extensive surface area for drug conjugation or entrapment, making them ideal for targeted and controlled delivery of phytochemicals. Nanocrystals are pure drug particles reduced to the nanometer scale, typically stabilized by surfactants or polymers. Their exceedingly high surface area enhances dissolution rates, which significantly improves the bioavailability of poorly soluble plant compounds like curcumin, silymarin, and resveratrol.

Nanofibers, produced mainly via electrospinning, are elongated, porous fiber structures with high surface area, capable of sustained release and tissue interaction. They find applications in wound healing, tissue regeneration, and localized drug delivery [11].

Mechanism of Action

Dendrimers

Dendrimers act primarily by encapsulating or conjugating phytochemicals through noncovalent interactions (such as hydrogen bonds or van der Waals forces) or covalent bonding. Their symmetrical, branched structure provides cavities capable of harbouring bioactive molecules, while terminal groups can be tailored for targeting or increasing biocompatibility. These molecules can cross cell membranes thanks to their nanosize, delivering phytochemicals effectively to intracellular targets. Surface modifications (like PEGylation or ligand attachment) can improve biocompatibility and targeting, reducing toxicity and mimicking natural cell interactions [12].

Nanocrystals

Reduced to nanometer dimensions, nanocrystals dramatically increase the surface area of the drug, thereby accelerating the dissolution process based on the principles of Noyes–Whitney and Ostwald–Freundlich equations. This leads to rapid absorption of poorly soluble phytochemicals in the gastrointestinal tract, enhancing their systemic availability. Stabilized with suitable surfactants, nanocrystals prevent agglomeration, offering a stable, high-energy form that can be absorbed efficiently [12].

Nanofibers

Nanofibers are produced through electrospinning, creating a high surface area, nanostructured matrix capable of loading phytochemicals either physically or chemically. When applied as wound dressings or tissue scaffolds, nanofibers enable controlled, sustained release of bioactives through diffusion or polymer erosion. Their fibrous network facilitates cell growth, proliferation, and tissue regeneration, making them therapeutic and regenerative agents simultaneously [12].

Table 01: Types of Nano-delivery systems in Phytopharmacetuicals

Nano carrier type	Phytochemical	Technique	Advantage	Application	Limitation
Polymeric NP (PLGA)	quercetin	Encapsulation	Enhanced bio availability	Cardio vascular disease	Limited clinical data
liposomes	curcumin	Nanovesicle	Improved stability	Anti oxidant	Scale up challenges
Solid lipid NP	resveratrol	Nano emulsion	Controlled release	Neuro protective	Cost of production
Nano gels	EGCG(green tea)	Gell based nano form	Sustained delivery	Anti cancer	Regulatory uncertainty
Nano emulsion	genstein	Emulsification	Increased solubility	Menopause management	Long term safety and known
neuosomes	silymarin	Surfactant vesicles	reduced toxicity	Liver protection	Stability in formulation
nanocrystals	berberine	Milling	enhanced permeability	Anti microbial	Reproducibility issue
Nano fibres	allicin	Electro spinning	Prolonged retention	Wound healing	Self life limitations
dentrimers	apigenin	Dentrimerization	Targeted delivery	Cardio protective	Possible cytotoxicity

Mechanisms Enhancing Efficacy

Improved Bioavailability

Nano carriers protect phytoconstituents from enzymatic degradation, enable mucosal uptake, and increase systemic circulation retention, ensuring effective delivery to target tissues [Fig 02].

- Protection from enzymatic degradation.
- Enhanced mucosal penetration and absorption.
- Increased plasma half-life.

Example: Quercetin nanoparticles increased oral bioavailability up to 10-fold compared to crude extract [13].

Controlled and Targeted Release:

Tailored release profiles reduce dosing frequency and minimize side effects. Nanocarriers can be designed for pH-sensitive, temperature-sensitive, or ligand-targeted release.

Example: Curcumin nanoparticles functionalized with folic acid target cancer cells overexpressing folate receptors.

Crossing Biological Barriers: Nanoparticles can cross the blood–brain barrier (BBB), enabling treatment of neurological disorders.

Example: Curcumin-loaded SLN improved memory in Alzheimer's models [14].

Multifunctional and Biocompatibility

Multifunctional and biocompatible carriers-plant-derived nanoparticles (PNPs)-are eco-friendly, biocompatible, and allow for multifunctional applications, including antimicrobial and antioxidant therapies.

Plant-derived nanoparticles (PNPs) act as both carrier and therapeutic agent, providing antioxidant or antimicrobial activity alongside drug delivery [15].

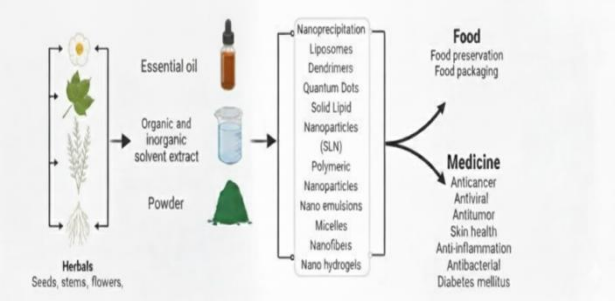

Fig 02: Mechanisms Enhancing Efficacy

Therapeutic Applications

Anticancer

Nanoformulations of curcumin, triploids, and berberine have shown enhanced cytotoxicity and tumour inhibition in preclinical studies.

Curcumin Nanoparticles: Enhanced cytotoxicity against breast and colon cancer cell lines.

Berberine Nanocrystals: Improved antitumor efficacy with reduced toxicity.

Resveratrol SLN: Potent apoptosis induction in prostate cancer models [16].

Hepatoprotection and Antioxidant

Quercetin phyto-nanoparticles demonstrate improved liver protection and antioxidant activity.

Quercetin nanoparticles: Demonstrated strong liver-protective effects in alcohol-induced hepatotoxicity models.

Silymarin nanoemulsions: Improved liver regeneration in patients with chronic liver disease [16].

Antimicrobial and Anti-inflammatory

Nanocarriers increase the efficacy of plant-based antimicrobials and anti-inflammatory agents, broadening their clinical potential.

Nanoformulations of Allicin and EGCG showed improved antibacterial activity against resistant strains.

Turmeric nano gels used in topical creams enhanced wound healing by reducing inflammation [17].

CNS and Chronic Diseases

Enhanced brain delivery and bioavailability of phytochemicals like curcumin have been reported, promising improved therapeutic outcomes in neurodegenerative and metabolic disorders.

Curcumin SLN and resveratrol nanoliposomes improved neuronal survival and memory functions in Alzheimer's disease. Ginseng phytosomes showed enhanced neuroprotection in Parkinson's models [18].

Challenges and Future Directions

Despite significant progress, several hurdles persist

Standardization

Achieving reproducible synthesis and characterization of nano-phytopharmaceuticals remains a barrier to clinical translation. Lack of uniform synthesis methods, leading to batch-to-batch variability.

Toxicity and Biocompatibility

Comprehensive toxicological profiling is crucial for safety assessment.

Potential risks of nanomaterials, such as ROS generation, immune reactions, and accumulation in organs [19].

Regulatory Frameworks

Globally harmonized guidelines are necessary to foster clinical acceptance and commercialization.

No harmonized guidelines for nano-herbal medicines.

Need for clear classification: dietary supplements vs. drugs [19].

Scalability and Cost

Developing cost-effective, scalable green synthesis routes for PNPs is a priority. High cost of nanoparticle synthesis limits commercialization.

Future Focus: green synthesis techniques using plant extracts as reducing agents [20].

Conclusion

Nanotechnology has emerged as a transformative tool in the field of phytopharmaceuticals, offering innovative solutions to overcome many of the limitations associated with conventional plant-based drug delivery systems. By engineering nanoscale carriers such as solid lipid nanoparticles, polymeric nanoparticles, liposomes, and phytosomes, we can enhance the stability, bioavailability, and therapeutic efficiency of bioactive plant compounds that are often poorly soluble or easily degraded. These nanocarriers enable more precise targeting of diseased tissues, thereby reducing side effects and improving patient outcomes through controlled and sustained release mechanisms. Furthermore, nanotechnology-based delivery systems can preserve the natural integrity of

phytochemicals, protect them from premature metabolism, and enable lower dosages for the same therapeutic effect, promoting safety and cost-effectiveness. Beyond clinical benefits, these approaches offer environmentally friendly alternatives by utilizing biodegradable and biocompatible materials, contributing to sustainable healthcare solutions. As research advances, nanotechnology will continue to redefine the potential of herbal medicines, bridging traditional wisdom with modern scientific innovation, and paving the way for a new era of efficient, targeted, and eco-conscious phytopharmaceutical therapies.

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Author Contribution
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