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Phytopharmacology in the Nanotech Era: Connecting Natural Compounds with Pharmaceutical Nanocarriers

Nikita Singh[1], Mohit Kumar Sahu[1], Bhushan Lal[1], Ajita Khichariya[1], Vinay Sagar Verma[1*]

[1]Kamla Institute of Pharmaceutical Sciences, Junwani, Bhilai, C.G. 490020.

***Corresponding Author E-mail: vinaysagarverma@gmail.com**

Abstract:

Phytopharmacology explores bioactive compounds derived from plants with diverse therapeutic potentials, including anticancer, neuroprotective, anti-inflammatory, and antimicrobial effects. Despite their promise, many phytochemicals suffer from poor solubility, instability, and suboptimal pharmacokinetics, limiting clinical translation. Nanotechnology-based delivery systems—such as lipid-based, polymeric, inorganic, and hybrid nanocarriers—offer transformative solutions by enhancing solubility, stability, targeted delivery, and controlled release of phytochemicals. These nanocarriers can be engineered for passive and active targeting, enabling improved bioavailability, tissue specificity, and therapeutic efficacy while minimizing off-target effects. Advanced strategies incorporating stimuli-responsive release, biomimetic coatings, and AI-driven design further refine these platforms for personalized medicine. Challenges remain in scale-up, reproducibility, regulatory compliance, and safety, necessitating interdisciplinary collaboration. Continued innovation in nanocarrier formulation promises to bridge traditional plant-based medicines with modern precision therapeutics, offering safer and more effective natural compound-based treatments.

Keywords:

Phytopharmacology, Bioactive Phytochemicals, Nanocarriers, Lipid Nanoparticles, Polymeric Nanoparticles, Controlled Release, Targeted Delivery, Nanomedicine, Stimuli-Responsive Systems, Biomimetic Nanocarriers, AI-Driven Design, Personalized Medicine, Natural Therapeutics.

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1. Introduction

Phytopharmacology, the study of bioactive compounds derived from plants and their pharmacological applications, has been a cornerstone of traditional and modern medicine for

centuries. Plant-derived compounds, often referred to as phytochemicals, encompass a wide array of chemical entities including alkaloids, flavonoids, terpenoids, polyphenols, and saponins, each exhibiting diverse biological activities. These natural products have been extensively explored for their therapeutic potential in the management of cancer, cardiovascular disorders, neurodegenerative diseases, inflammatory conditions, and infectious diseases. Their multifaceted mechanisms of action, ranging from modulation of cellular signaling pathways to antioxidant and immunomodulatory effects, make them invaluable candidates for drug development [1-2]. Despite their immense promise, conventional phytopharmaceuticals face several critical challenges that have hindered their clinical translation. Many phytochemicals exhibit poor aqueous solubility, which limits their absorption and oral bioavailability. Others are chemically unstable under physiological conditions, undergoing rapid degradation or metabolic transformation that reduces their therapeutic efficacy. Additionally, the pharmacokinetics of many natural compounds are suboptimal, with short systemic half-lives and rapid clearance, necessitating frequent dosing and increasing the risk of side effects. These limitations not only restrict the clinical utility of plant-derived therapeutics but also complicate the design of effective and reliable drug formulations [3-4].

In response to these challenges, nanotechnology has emerged as a transformative approach for enhancing the delivery, stability, and therapeutic efficiency of phytochemicals. Nanocarriers, including lipid-based systems, polymeric nanoparticles, inorganic nanomaterials, and hybrid constructs, offer unique advantages for encapsulating and transporting bioactive plant compounds to their site of action. By reducing particle size to the nanoscale, these systems increase surface area and solubility, enhance cellular uptake, and facilitate targeted delivery, thereby overcoming some of the inherent limitations of traditional formulations. Moreover, nanocarriers can provide controlled and sustained release of phytochemicals, protecting them from enzymatic degradation and premature metabolism. This allows for prolonged systemic circulation and improved bioavailability, which is particularly important for compounds with otherwise poor pharmacokinetic profiles. The versatility of nanocarrier platforms also enables the functionalization of surfaces with targeting ligands, such as antibodies, peptides, or aptamers, to achieve tissue- or cell-specific delivery, further enhancing therapeutic outcomes while minimizing off-target effects. These strategies have shown significant promise in preclinical studies, demonstrating enhanced anticancer activity, improved neuroprotective effects, and increased antimicrobial potency of various phytochemicals [5-6].

The integration of nanotechnology with phytopharmacology also aligns with the broader movement toward precision medicine and personalized therapeutics. By tailoring nanocarrier design to the physicochemical properties of specific phytochemicals, as well as to patient-specific parameters such as metabolism and disease state, researchers can develop more effective and individualized treatment regimens. For instance, hybrid nanocarriers combining lipid and polymeric matrices can be optimized to release multiple phytochemicals in a temporally controlled manner, allowing synergistic effects against complex disease pathways. Similarly, stimuli-responsive nanocarriers that release payloads in response to pH, temperature, or enzymatic activity can ensure that bioactive compounds are delivered precisely where and when they are needed, reducing systemic exposure and potential toxicity. The adaptability of

these systems represents a significant advancement over conventional drug delivery approaches, where formulation limitations often prevent optimal therapeutic performance [7-8].

Despite the growing interest in nano-phytopharmacology, several challenges remain in translating these innovations from bench to bedside. Factors such as large-scale reproducibility, long-term stability, biocompatibility, and regulatory compliance must be carefully addressed to ensure safe and effective clinical application. Additionally, the heterogeneity of natural extracts, variability in phytochemical content, and potential interactions with other drugs or biological systems add layers of complexity to formulation design. As a result, interdisciplinary collaboration between phytochemists, nanotechnologists, pharmacologists, and clinicians is essential to develop robust, reproducible, and clinically translatable nanoformulations. The aim is not only to enhance the therapeutic potential of individual phytochemicals but also to create combinatorial platforms that can target multiple disease mechanisms simultaneously.

This review aims to provide a comprehensive overview of the current state of phytopharmacology in the nanotechnology era, highlighting how pharmaceutical nanocarriers are bridging the gap between natural bioactive compounds and effective clinical therapeutics. Specifically, the paper explores the classification and therapeutic potential of key phytochemicals, examines the variety of nanocarrier platforms available for their delivery, and discusses mechanistic insights into nanocarrier-mediated enhancements in solubility, bioavailability, and targeting. Furthermore, it addresses pharmacokinetic considerations, therapeutic applications across major disease areas, and critical safety and regulatory aspects relevant to phytopharmaceutical nanomedicines. By synthesizing recent advances and challenges, this review seeks to provide a roadmap for future research and development in this interdisciplinary field, emphasizing the integration of nanotechnology, plant science, and pharmaceutical formulation to realize the full clinical potential of phytochemicals. Through such efforts, next-generation nanomedicines may harness the vast chemical diversity of plant compounds to offer safer, more effective, and patient-friendly therapeutic options across a spectrum of human diseases [9-10].

2: Phytochemicals and Their Therapeutic Potential

Phytochemicals, the biologically active compounds derived from plants, constitute a vast and structurally diverse group of molecules that have been widely explored for their pharmacological activities. These naturally occurring compounds can be broadly classified into several categories based on their chemical structures, including alkaloids, flavonoids, terpenoids, polyphenols, and saponins. Alkaloids, which are nitrogen-containing compounds, are renowned for their potent pharmacological effects, ranging from anticancer and antimalarial activity to neuroprotective properties. Examples include vincristine and vinblastine, extracted from *Catharanthus roseus*, which are clinically used as chemotherapeutic agents, and berberine, derived from *Berberis* species, with notable antimicrobial and cardioprotective effects. Flavonoids, a large class of polyphenolic compounds, exhibit strong antioxidant, anti-inflammatory, and anti-carcinogenic properties. Well-studied examples include quercetin, kaempferol, and epigallocatechin gallate (EGCG), which have shown efficacy in modulating cellular oxidative stress, inhibiting tumor growth, and supporting cardiovascular health [11-12]. Terpenoids, derived from isoprene units, include

monoterpenes, diterpenes, and triterpenes, and possess antimicrobial, anticancer, and anti-inflammatory activities; notable examples include paclitaxel, a diterpenoid used in cancer therapy, and ginkgolides from *Ginkgo biloba*, which have neuroprotective properties. Polyphenols, encompassing compounds like resveratrol and curcumin, are known for their antioxidant potential and ability to modulate multiple signaling pathways involved in inflammation, cancer, and metabolic disorders. Saponins, glycosidic compounds with both hydrophilic and lipophilic properties, have demonstrated immune-modulatory, anticancer, and hepatoprotective effects. Together, these phytochemicals represent a treasure trove of bioactive molecules with diverse therapeutic applications.

The pharmacological potential of phytochemicals spans a wide spectrum of disease management areas. In oncology, numerous plant-derived compounds exert anti-proliferative, pro-apoptotic, and anti-metastatic effects. Curcumin, resveratrol, quercetin, and epigallocatechin gallate, among others, have demonstrated efficacy in preclinical cancer models by regulating signaling pathways such as NF-κB, PI3K/Akt/mTOR, and MAPK, which are critical for tumor cell survival, proliferation, and angiogenesis. In addition to anticancer activity, phytochemicals are recognized for their anti-inflammatory properties. Chronic inflammation underlies many diseases, including arthritis, cardiovascular disorders, and neurodegenerative conditions. Compounds such as kaempferol, luteolin, and boswellic acid inhibit pro-inflammatory cytokines, modulate cyclooxygenase and lipoxygenase pathways, and attenuate oxidative stress, thus providing a multifaceted approach to inflammation management. Antimicrobial activity is another significant therapeutic feature of plant-derived molecules. Alkaloids, terpenoids, and polyphenols exhibit antibacterial, antiviral, antifungal, and antiparasitic effects through mechanisms such as disruption of microbial membranes, inhibition of nucleic acid synthesis, and suppression of quorum sensing, making them potential alternatives or adjuncts to conventional antibiotics in the face of increasing antimicrobial resistance. Neuroprotective and cardioprotective effects have also been extensively reported [13-14]. For example, ginkgolides and bacosides enhance cognitive function and synaptic plasticity, while resveratrol, epigallocatechin gallate, and berberine provide cardiovascular benefits through antioxidative, anti-inflammatory, and lipid-modulating mechanisms. Collectively, these pharmacological activities underscore the therapeutic versatility of phytochemicals and their relevance in modern drug discovery.

Despite their immense potential, the clinical translation of phytochemicals is significantly hampered by pharmacokinetic and biopharmaceutical limitations. Many plant-derived compounds exhibit low aqueous solubility, poor stability under physiological conditions, and rapid metabolic degradation, which together contribute to low oral bioavailability. Curcumin, for instance, demonstrates potent pharmacological activity in vitro but suffers from extremely poor systemic absorption and rapid metabolism, limiting its clinical effectiveness. Similarly, resveratrol undergoes rapid glucuronidation and sulfation, leading to transient plasma levels that are insufficient to exert sustained therapeutic effects. Low membrane permeability further constrains the intracellular accumulation of several phytochemicals, reducing their efficacy in targeting specific tissues or cellular compartments. Moreover, rapid clearance from systemic circulation often necessitates frequent dosing, which can increase the risk of side effects and reduce patient compliance. These challenges are further compounded by the inherent

variability in natural extracts, which can result in inconsistent phytochemical content, unpredictable pharmacokinetics, and variable therapeutic outcomes. Such limitations highlight the critical need for advanced delivery strategies that can enhance solubility, protect phytochemicals from premature degradation, improve bioavailability, and enable targeted delivery to the desired site of action [15-16].

To overcome these challenges, there has been a growing interest in integrating phytochemicals with advanced drug delivery platforms, particularly nanocarriers, which can provide physicochemical stabilization, controlled release, and enhanced tissue targeting. Nanotechnology-based formulations not only improve solubility and pharmacokinetic profiles but also enable surface functionalization with ligands for active targeting of specific cells or tissues. This approach has shown promising results in preclinical studies, demonstrating increased accumulation of phytochemicals in tumor tissues, enhanced penetration across biological barriers such as the blood–brain barrier, and sustained therapeutic activity with reduced systemic toxicity. Moreover, nanocarrier systems allow for combination strategies, wherein multiple phytochemicals or phytochemical–drug conjugates can be co-delivered to achieve synergistic therapeutic effects, further expanding the clinical potential of plant-derived compounds [17].

3: Nanocarrier Platforms for Phytopharmacology

Nanocarrier systems have emerged as transformative platforms for enhancing the therapeutic efficacy of phytochemicals, addressing many of the biopharmaceutical challenges associated with plant-derived compounds, such as poor solubility, low stability, and limited bioavailability. Among the various nanocarrier types, lipid-based nanocarriers have received considerable attention for their ability to encapsulate both hydrophilic and lipophilic phytochemicals, providing enhanced solubility, improved absorption, and targeted delivery. Liposomes, one of the earliest and most widely studied lipid-based carriers, are vesicular structures composed of phospholipid bilayers that can encapsulate hydrophilic molecules in their aqueous core and lipophilic compounds within the lipid bilayer. This unique architecture enables the protection of sensitive phytochemicals from enzymatic degradation and facilitates controlled release at the target site. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) represent advanced lipid-based platforms, offering enhanced stability, sustained release profiles, and improved drug loading compared to conventional liposomes. SLNs consist of solid lipids that maintain their solid state at both room and body temperature, providing a rigid matrix for encapsulated phytochemicals, while NLCs incorporate liquid lipid components into the solid lipid matrix, creating imperfections that increase drug loading capacity and release modulation [18-19]. Additionally, phytosome formulations, which involve complexation of phytochemicals with phospholipids, have demonstrated superior bioavailability and enhanced membrane permeability, particularly for polyphenolic compounds such as curcumin, quercetin, and silybin. These lipid-based carriers have also been engineered for active targeting through surface modification with ligands like folate, transferrin, or antibodies, enabling preferential accumulation in diseased tissues such as tumors or inflamed sites, thereby minimizing off-target effects.

Polymeric nanoparticles are another versatile nanocarrier platform for phytopharmaceutical delivery. These carriers are typically composed of biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, polyethylene glycol (PEG)-modified systems, and polycaprolactone (PCL). Biodegradable polymers offer the advantage of controlled and sustained release of phytochemicals through gradual polymer degradation, which not only prolongs therapeutic activity but also reduces dosing frequency and associated systemic toxicity. Surface modification of polymeric nanoparticles enables targeted delivery to specific tissues or cell types; for example, chitosan-based nanoparticles can be functionalized with ligands to enhance mucoadhesion or facilitate crossing of biological barriers like the intestinal epithelium or the blood-brain barrier [20-21]. PLGA nanoparticles, due to their well-established safety profile and tunable degradation rates, have been widely explored for encapsulating anticancer phytochemicals such as curcumin, resveratrol, and quercetin, providing controlled release and improved intracellular uptake in tumor models. Furthermore, PEGylation of polymeric nanoparticles can reduce recognition by the mononuclear phagocyte system, prolonging circulation time and enhancing bioavailability of phytochemicals, a strategy particularly valuable for compounds with rapid systemic clearance.

Inorganic nanocarriers, including gold, silica, and magnetic nanoparticles, have expanded the horizon of phytopharmaceutical delivery by offering unique physicochemical and optical properties that enable multifunctional applications. Gold nanoparticles (AuNPs) exhibit excellent biocompatibility and facile surface functionalization, allowing conjugation with phytochemicals for targeted delivery or photothermal therapy. Silica nanoparticles provide a highly porous and tunable surface area, suitable for loading substantial amounts of bioactive plant-derived compounds while permitting controlled release. Magnetic nanoparticles, such as iron oxide-based systems, enable external magnetic field-guided targeting and have been combined with phytochemicals for theranostic applications, integrating therapeutic and diagnostic functionalities. These inorganic carriers also allow the incorporation of imaging agents, enabling simultaneous tracking of phytochemical distribution and therapeutic efficacy in vivo, which is critical for optimizing dosage and monitoring treatment outcomes. Moreover, inorganic nanocarriers can be engineered to respond to external stimuli such as pH, temperature, or magnetic fields, facilitating controlled and site-specific release of phytochemicals in targeted tissues [22-23].

Hybrid and biomimetic nanocarriers represent the cutting edge of phytopharmaceutical delivery, combining the advantages of different materials while mimicking natural biological systems. Lipid–polymer hybrid nanoparticles, for example, integrate the biocompatibility and targeting potential of lipids with the structural stability and controlled release properties of polymers, resulting in carriers capable of efficient encapsulation, prolonged circulation, and precise delivery of phytochemicals. Biomimetic systems, such as cell membrane-coated nanoparticles, harness membranes from erythrocytes, platelets, or leukocytes to confer immune evasion, prolonged circulation, and tissue-specific homing, which is particularly beneficial for phytochemicals that are sensitive to rapid clearance or enzymatic degradation. Exosome-mimetic carriers, derived from natural extracellular vesicles, offer another layer of biological compatibility and inherent targeting capabilities, enabling efficient delivery of phytochemicals across cellular barriers while minimizing immunogenic responses. These hybrid and

biomimetic strategies enhance the pharmacokinetic profile of phytochemicals and broaden their therapeutic applicability, ranging from anticancer and anti-inflammatory applications to neuroprotective and cardioprotective effects.

Overall, the selection of an appropriate nanocarrier platform is critical for the successful translation of phytochemicals into effective therapeutics. Lipid-based nanocarriers provide excellent solubility and membrane compatibility, polymeric nanoparticles offer sustained and controlled release with customizable targeting, inorganic carriers facilitate theranostic applications and external stimuli responsiveness, and hybrid/biomimetic systems combine the strengths of multiple materials with enhanced biocompatibility and immune evasion. Each platform addresses specific limitations of conventional phytopharmaceuticals, such as poor solubility, low stability, and rapid clearance, while offering opportunities for targeted delivery and personalized therapy. The choice of carrier depends on the physicochemical properties of the phytochemical, the intended therapeutic application, and the desired pharmacokinetic profile [24-25].

4: Mechanisms of Nanocarrier-Mediated Phytochemical Delivery

The mechanisms by which nanocarriers enhance the delivery and therapeutic efficacy of phytochemicals are multifaceted, addressing fundamental limitations of conventional plant-derived drug systems, including low solubility, poor absorption, rapid metabolism, and limited bioavailability. One of the primary mechanisms is the enhancement of solubility and absorption. Many phytochemicals, particularly polyphenols, terpenoids, and alkaloids, are poorly water-soluble, which severely restricts their oral bioavailability and systemic therapeutic potential. Nanocarrier encapsulation significantly improves solubility by dispersing the hydrophobic compounds within lipid matrices, polymeric networks, or hybrid nanostructures. Liposomes, for instance, can encapsulate hydrophilic and hydrophobic molecules simultaneously, providing a protective aqueous or lipid environment that allows the phytochemical to remain in solution and resist precipitation under physiological conditions. Similarly, polymeric nanoparticles, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) increase solubility by creating a nanometric environment that reduces aggregation, enhances dispersion, and improves interaction with biological membranes. Enhanced solubility, combined with nanoscale particle size, facilitates improved absorption across biological barriers, including intestinal mucosa and skin, due to increased surface area and improved interaction with transport pathways [26-27].

Controlled and sustained release represents another critical mechanism underlying nanocarrier-mediated delivery. Conventional phytochemicals often suffer from rapid degradation or clearance, necessitating frequent dosing and limiting therapeutic efficacy. Nanocarriers can provide sustained release through degradation-controlled or diffusion-controlled mechanisms. In polymeric systems, such as PLGA and chitosan nanoparticles, the phytochemical is released gradually as the polymer matrix undergoes hydrolytic or enzymatic degradation. This slow and continuous release maintains therapeutic plasma levels over extended periods, reducing dosing frequency and minimizing systemic toxicity. Lipid-based carriers, such as SLNs and NLCs, utilize lipid diffusion mechanisms for sustained release, wherein the encapsulated phytochemical diffuses gradually from the lipid core into surrounding biological fluids. Hybrid

carriers, integrating polymeric and lipid components, combine these mechanisms to provide highly tunable release kinetics, allowing precise control over the timing and rate of phytochemical delivery. Controlled release not only ensures prolonged pharmacological activity but also minimizes burst release, which can be toxic or cause off-target effects, particularly for potent phytochemicals with narrow therapeutic indices.

Targeted delivery is a major advantage of nanocarrier-mediated systems, enabling both passive and active targeting of phytochemicals to specific tissues, cells, or subcellular compartments. Passive targeting exploits the inherent physicochemical characteristics of nanoparticles, such as size, shape, and surface charge, to accumulate preferentially in diseased tissues through mechanisms like the enhanced permeability and retention (EPR) effect in tumors or inflamed tissues. For example, nanoparticles sized 50–200 nm can penetrate leaky tumor vasculature and accumulate within the tumor microenvironment, delivering encapsulated anticancer phytochemicals such as curcumin or resveratrol directly to malignant cells. Active targeting involves functionalization of the nanoparticle surface with ligands such as antibodies, peptides, carbohydrates, or aptamers that selectively bind to receptors expressed on target cells. This strategy enhances cellular uptake through receptor-mediated endocytosis, ensuring that the phytochemical reaches its site of action while sparing healthy tissues. Additionally, hybrid and biomimetic carriers, including cell membrane-coated nanoparticles and exosome-mimetic vesicles, leverage natural homing and immune-evasion mechanisms to further refine targeting efficiency, enabling delivery of phytochemicals to otherwise inaccessible sites such as the central nervous system or intracellular organelles [28-29].

Nanocarriers also protect phytochemicals from enzymatic degradation and metabolic clearance, a major limitation of conventional formulations. Many plant-derived compounds are susceptible to rapid metabolism by hepatic enzymes, degradation by gut microbiota, or chemical instability in biological fluids. Encapsulation within nanocarriers shields the phytochemical from these adverse conditions, preserving structural integrity and bioactivity until it reaches the target site. Lipid-based carriers, for instance, form a protective bilayer or core-shell structure around the phytochemical, preventing exposure to degradative enzymes and pH fluctuations. Polymeric nanoparticles can similarly encapsulate the compound within a biodegradable polymer network, releasing the payload only after partial degradation or in response to specific stimuli such as pH changes or enzymatic activity at the target site. Furthermore, surface functionalization with hydrophilic polymers like polyethylene glycol (PEG) reduces opsonization and clearance by the mononuclear phagocyte system, prolonging systemic circulation and enhancing bioavailability.

An additional mechanism involves the modulation of cellular uptake pathways. Nanocarriers can facilitate endocytosis, transcytosis, or receptor-mediated internalization of phytochemicals, improving intracellular bioavailability, which is particularly important for compounds that act on intracellular targets. Surface charge plays a significant role here; cationic nanoparticles can interact favorably with negatively charged cell membranes, enhancing uptake, while zwitterionic or neutral coatings can minimize non-specific interactions and improve circulation time. Nanocarriers can also exploit specific intracellular trafficking pathways, such as lysosomal escape or nuclear targeting, to ensure that the phytochemical reaches its intracellular target, maximizing therapeutic efficacy.

Finally, the integration of smart or stimuli-responsive features into nanocarriers adds an additional layer of control over phytochemical delivery. Nanocarriers can be engineered to respond to internal stimuli such as pH, redox gradients, or enzymatic activity, or to external triggers like light, ultrasound, or magnetic fields, allowing site-specific release in response to pathological conditions. For example, pH-sensitive polymeric nanoparticles can release anti-inflammatory phytochemicals specifically in acidic inflammatory tissues, while thermosensitive lipid carriers may release anticancer phytochemicals upon mild hyperthermia applied to tumor sites. These mechanisms not only enhance the therapeutic index of phytochemicals but also reduce systemic exposure and potential side effects.

In summary, nanocarrier-mediated delivery significantly improves the pharmacological performance of phytochemicals by enhancing solubility and absorption, providing controlled and sustained release, enabling passive and active targeting, and protecting compounds from enzymatic degradation and metabolic clearance. These mechanisms collectively overcome the inherent limitations of conventional phytopharmaceuticals, offering the potential for higher efficacy, reduced toxicity, and broader clinical applicability. Rational design of nanocarriers, tailored to the physicochemical properties of the phytochemical and the intended therapeutic application, is key to optimizing these mechanisms [30-31]. Figure 1

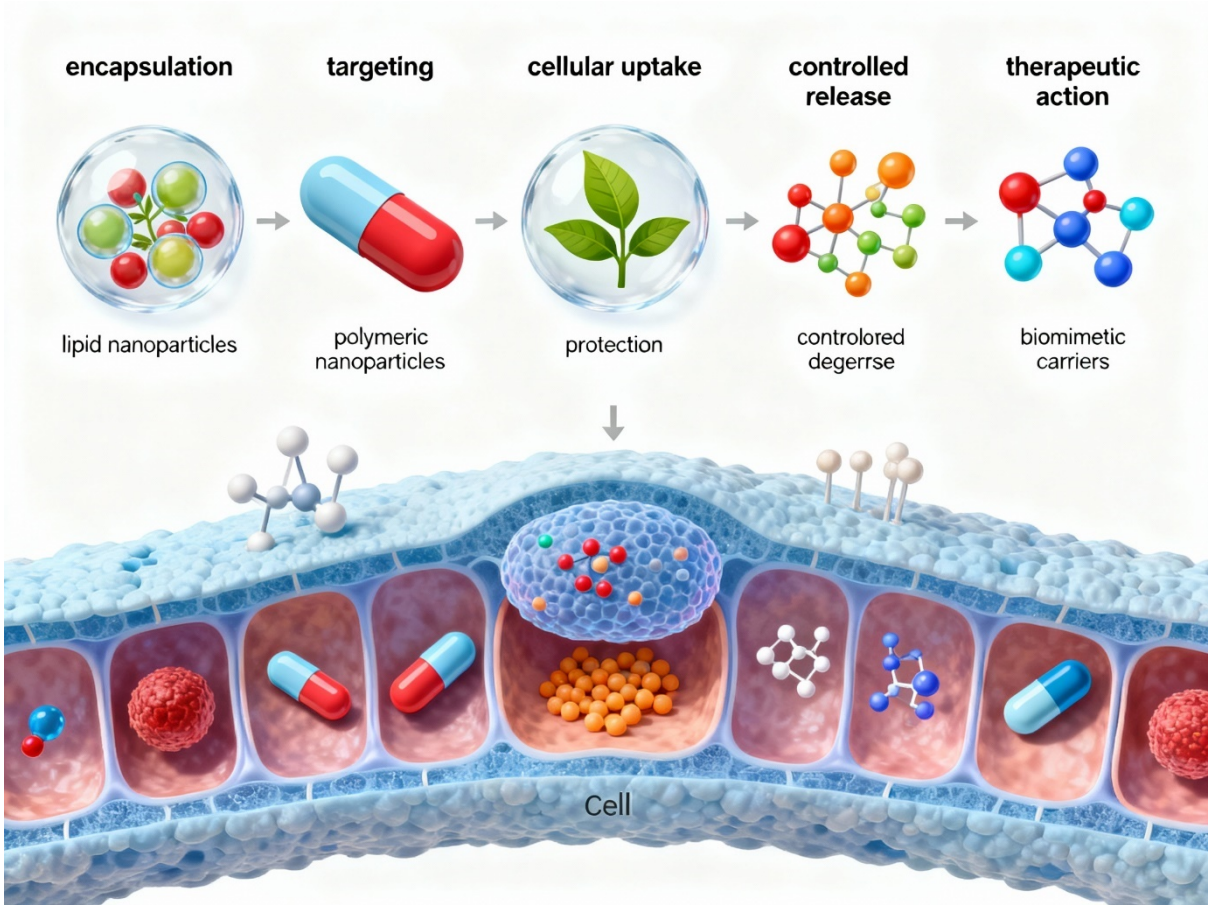

Figure 1: Mechanistic illustration of nanocarrier-mediated phytochemical delivery.

5: Pharmacokinetics, Biodistribution, and Bioavailability

The pharmacokinetics, biodistribution, and bioavailability of phytochemicals are profoundly influenced by the use of nanocarrier systems, which provide solutions to the longstanding challenges of poor solubility, rapid metabolism, and limited systemic circulation inherent to conventional plant-derived compounds. The size, surface charge, and chemical composition of nanocarriers play pivotal roles in determining their absorption, distribution, metabolism, and excretion (ADME) profiles, directly affecting the therapeutic potential of encapsulated phytochemicals. Nanoparticles within the size range of 10–200 nm are generally optimal for systemic delivery, as they can efficiently evade renal clearance while also avoiding rapid uptake by the reticuloendothelial system (RES). Small nanoparticles below 10 nm are typically cleared quickly via renal filtration, whereas particles exceeding 200 nm may be sequestered by macrophages in the liver and spleen, reducing bioavailability. Surface charge is another critical factor; cationic nanocarriers interact more effectively with negatively charged cell membranes, enhancing cellular uptake, but may also induce cytotoxicity and opsonization, leading to faster clearance. Neutral or PEGylated surfaces often strike a balance between prolonged circulation and minimal immune recognition, facilitating passive targeting via the enhanced permeability and retention (EPR) effect in tumors or inflamed tissues.

Nanocarrier composition, including the use of biodegradable polymers, lipids, and hybrid materials, significantly influences metabolic stability and drug release kinetics. For instance, PLGA and chitosan nanoparticles degrade gradually in physiological conditions, protecting phytochemicals from enzymatic hydrolysis in the gastrointestinal tract or systemic circulation. Lipid-based carriers such as liposomes, SLNs, and NLCs provide additional protection by encapsulating hydrophobic phytochemicals within lipid bilayers or solid lipid matrices, preventing premature release and maintaining structural integrity. Surface functionalization, such as PEGylation or ligand attachment, not only improves biocompatibility but also reduces opsonization and RES-mediated clearance, prolonging circulation half-life and improving tissue accumulation. Collectively, these design considerations enhance the systemic availability of phytochemicals, allowing for lower dosing frequencies and improved patient compliance [32-33].

Biodistribution studies further demonstrate the advantages of nanocarrier-mediated delivery. Upon systemic administration, nanocarriers can selectively accumulate in target tissues through passive or active targeting mechanisms. Passive targeting relies on size- and permeability-dependent extravasation in diseased tissues, such as tumors, where the leaky vasculature allows nanoparticles to preferentially localize. Active targeting involves surface modification with ligands such as antibodies, peptides, or aptamers that recognize specific receptors on target cells, thereby enhancing cellular uptake and intracellular delivery. For example, curcumin-loaded PLGA nanoparticles functionalized with folic acid have shown preferential accumulation in tumor tissues due to folate receptor-mediated endocytosis, while resveratrol nanoparticles conjugated with transferrin exhibit improved brain delivery across the blood–brain barrier (BBB). Such targeted biodistribution not only increases therapeutic efficacy but also reduces off-target side effects by limiting systemic exposure.

Nanocarriers also significantly improve the oral bioavailability of phytochemicals, which is often limited by poor solubility, chemical instability, or extensive first-pass metabolism in the liver. Encapsulation within nanoparticles protects these compounds from degradation in the acidic gastric environment or enzymatic hydrolysis in the intestine. Furthermore, the nanoscale size facilitates enhanced absorption through transcellular or paracellular pathways and can exploit carrier-mediated transport mechanisms. Studies have shown that quercetin-loaded SLNs, for instance, exhibit higher plasma concentrations and prolonged circulation compared to free quercetin, indicating improved systemic bioavailability. Similarly, curcumin encapsulated in polymeric or lipid-based nanoparticles demonstrates enhanced oral absorption and bioactivity in both in vitro and in vivo models, highlighting the clinical relevance of nanocarrier-mediated delivery in overcoming traditional pharmacokinetic barriers.

In vitro–in vivo correlation (IVIVC) studies provide additional insights into the performance of nanocarrier systems. Such studies evaluate the relationship between nanoparticle characteristics, release kinetics, and observed pharmacokinetic parameters. For example, in vitro release assays may demonstrate controlled and sustained release of phytochemicals from polymeric nanoparticles, which is mirrored by prolonged plasma concentrations and reduced clearance rates in animal models. Similarly, in vitro cell uptake and cytotoxicity studies often correlate with enhanced tissue distribution and therapeutic outcomes in vivo. These correlations are essential for optimizing nanocarrier formulations and predicting clinical performance, enabling rational design approaches that maximize efficacy while minimizing toxicity. Advanced analytical techniques, including fluorescence imaging, radiolabeling, and mass spectrometry, are commonly employed to track the biodistribution and pharmacokinetics of nanocarrier-loaded phytochemicals, providing detailed information on tissue-specific accumulation, metabolic pathways, and clearance rates [34-35].

The influence of nanocarrier size, surface charge, and composition on ADME is further exemplified by comparative studies of free versus encapsulated phytochemicals. Free curcumin exhibits extremely low oral bioavailability due to poor solubility and rapid metabolism; however, when encapsulated within PLGA or lipid-based nanoparticles, bioavailability increases several-fold, plasma half-life is extended, and systemic exposure is significantly enhanced. Similarly, resveratrol, quercetin, and other flavonoids demonstrate improved tissue penetration, delayed clearance, and greater therapeutic efficacy when delivered via nanocarriers. Such improvements are not only due to enhanced solubility and stability but also result from the controlled release profile and targeted delivery afforded by nanocarrier systems.

Overall, the pharmacokinetic and biodistribution advantages of nanocarrier-mediated phytochemical delivery provide a solid foundation for their enhanced bioavailability and therapeutic efficacy. By rationally designing nanoparticles with optimized size, charge, composition, and surface functionality, it is possible to overcome the limitations of conventional phytopharmaceuticals and achieve targeted, sustained, and efficient delivery. These properties are particularly valuable for compounds with poor intrinsic bioavailability or rapid metabolic clearance, enabling lower dosing frequencies, improved therapeutic outcomes, and reduced systemic toxicity. In conjunction with in vitro–in vivo correlation studies, these strategies facilitate the translation of nanocarrier-based phytochemicals from bench to bedside,

establishing a framework for next-generation plant-derived therapeutics with predictable and reproducible pharmacokinetic profiles [36-37].

6: Therapeutic Applications

The therapeutic potential of phytochemicals is greatly amplified when integrated with nanocarrier systems, addressing the traditional limitations of plant-derived compounds such as poor solubility, rapid metabolism, and low bioavailability. Among the most explored applications is anticancer therapy, where natural compounds like curcumin, resveratrol, and quercetin exhibit potent antiproliferative, pro-apoptotic, and antiangiogenic activities. However, the clinical translation of these compounds is often hindered by their hydrophobicity, poor systemic circulation, and rapid clearance from the body. Nanoparticle-based delivery systems offer a transformative solution by encapsulating these bioactive molecules into biodegradable polymeric nanoparticles, lipid-based carriers, or hybrid nanostructures, ensuring sustained release and improved tumor accumulation. Targeting strategies, such as surface modification with folate, transferrin, or tumor-homing peptides, facilitate receptor-mediated uptake by cancer cells, enhancing selective cytotoxicity while sparing healthy tissues. Studies demonstrate that curcumin-loaded PLGA nanoparticles or liposomal formulations achieve higher tumor uptake, improved pharmacokinetics, and significant tumor growth inhibition in preclinical models, surpassing the efficacy of free curcumin. Similarly, resveratrol and quercetin nanoparticles show enhanced induction of apoptosis, inhibition of metastasis, and suppression of tumor angiogenesis, highlighting the potential of nanocarrier-mediated phytochemicals as adjunct or standalone anticancer therapies [38-39].

Beyond oncology, phytochemicals are increasingly leveraged for anti-inflammatory and antioxidant applications, addressing chronic conditions such as arthritis, cardiovascular disorders, and neuroinflammation. Flavonoids, terpenoids, and polyphenols possess potent radical-scavenging activities and the ability to modulate pro-inflammatory signaling pathways, but their systemic efficacy is often limited by poor solubility and enzymatic degradation. Encapsulation into nanocarriers, including solid lipid nanoparticles, polymeric micelles, and nanoemulsions, improves their bioavailability, prolongs systemic circulation, and allows targeted delivery to inflamed tissues. For instance, quercetin-loaded SLNs and naringenin nanomicelles exhibit enhanced accumulation at inflamed sites, sustained antioxidant activity, and significant reduction in pro-inflammatory cytokines in animal models. These delivery systems also mitigate the rapid clearance and metabolic instability of natural antioxidants, enabling prolonged therapeutic effects with lower doses, thereby improving safety profiles and patient compliance.

In the realm of antimicrobial and antiviral therapy, phytochemicals such as allicin, berberine, and catechins have shown broad-spectrum activity against bacteria, fungi, and viruses. Nevertheless, their clinical potential is often curtailed by poor absorption, low stability, and rapid systemic elimination. Nanocarrier systems provide protective matrices that enhance solubility, stabilize the bioactive molecules, and promote controlled release at infection sites. For example, berberine-loaded PLGA nanoparticles demonstrate improved penetration into bacterial biofilms, enhanced antimicrobial activity, and reduced minimum inhibitory concentrations compared to free berberine. Similarly, epigallocatechin gallate (EGCG)

encapsulated in lipid-based nanoparticles exhibits enhanced antiviral efficacy against influenza and herpes viruses by promoting targeted uptake and sustained intracellular delivery. Magnetic and gold nanoparticles functionalized with plant-derived antivirals not only provide therapeutic benefits but also enable theranostic applications, allowing simultaneous imaging and treatment of infected tissues. These advancements underscore the potential of nanocarrier-mediated phytochemicals in overcoming drug resistance, improving tissue penetration, and enhancing overall antimicrobial and antiviral effectiveness [40-41].

Furthermore, neuroprotective and cardioprotective applications of phytochemicals have garnered substantial attention, particularly in the context of chronic neurological disorders and cardiovascular diseases. Polyphenols such as resveratrol, curcumin, and catechins exert neuroprotective effects by attenuating oxidative stress, modulating neuroinflammatory pathways, and promoting neuronal survival. However, their therapeutic potential is limited by poor blood–brain barrier (BBB) penetration. Nanocarriers, particularly PEGylated polymeric nanoparticles, liposomes, and exosome-mimetic vesicles, facilitate enhanced BBB crossing via receptor-mediated transcytosis or adsorption-mediated uptake, improving brain bioavailability and therapeutic efficacy. In animal models of neurodegenerative diseases, resveratrol-loaded nanoparticles show improved cognitive function, reduced oxidative damage, and suppression of amyloid-beta accumulation, outperforming free compounds. Similarly, for cardioprotection, flavonoids and terpenoids encapsulated in lipid-based or polymeric nanoparticles demonstrate improved myocardial targeting, reduced oxidative stress, and attenuation of ischemia-reperfusion injury. Surface functionalization with cardiac-homing peptides or antibodies further enhances selective delivery to cardiac tissue, minimizing systemic exposure and reducing potential side effects. These findings collectively highlight the capacity of nanocarrier-mediated delivery to expand the therapeutic reach of phytochemicals into tissues and organs that are otherwise challenging to target [42-43].

Overall, nanotechnology-enabled delivery of phytochemicals represents a paradigm shift in plant-based therapeutics, bridging the gap between potent bioactive molecules and clinical efficacy. By enhancing solubility, stability, circulation time, and tissue-specific targeting, nanocarriers overcome the primary limitations that have historically hindered the translation of natural compounds into effective therapies. The versatility of nanocarriers—ranging from lipid-based, polymeric, and inorganic nanoparticles to hybrid and biomimetic systems—enables tailored delivery strategies for diverse therapeutic applications, including oncology, chronic inflammatory diseases, infectious diseases, and neurocardiovascular disorders. Furthermore, combinatorial approaches, such as co-delivery of multiple phytochemicals or integration with conventional drugs, can potentiate synergistic effects, reduce toxicity, and enhance patient outcomes. As the field progresses, continued advancements in nanoparticle design, functionalization, and characterization, coupled with in-depth pharmacokinetic and pharmacodynamic studies, will pave the way for the clinical translation of nanocarrier-mediated phytopharmaceuticals, fulfilling the promise of next-generation natural therapeutics [44-45].

7. Safety, Toxicity, and Regulatory Considerations

The integration of phytochemicals with nanocarriers brings tremendous therapeutic promise, yet safety and toxicity remain central concerns in their clinical translation. Biocompatibility assessments are critical to ensure that the nanocarrier itself does not elicit adverse cellular or systemic responses, independent of the encapsulated phytochemical. In vitro studies, including cytotoxicity assays, hemolysis tests, and inflammatory cytokine measurements, provide initial insights into the safety profile of nanocarrier formulations. However, these studies must be complemented by in vivo investigations assessing acute and chronic toxicity, biodistribution, and organ-specific accumulation. The surface chemistry, particle size, charge, and degradability of the nanocarrier significantly influence immunogenicity and off-target effects. For example, cationic polymeric nanoparticles may induce higher cytotoxicity or inflammatory responses compared to neutral or PEGylated carriers, whereas lipid-based carriers generally exhibit enhanced biocompatibility. Additionally, long-term exposure studies are essential to evaluate potential cumulative toxicity, particularly when nanocarriers are designed for chronic administration or controlled release of phytochemicals over extended periods. Environmental considerations are increasingly relevant as nanoparticle manufacturing, disposal, and excretion may introduce biologically active nanomaterials into ecosystems, raising concerns about ecological toxicity and bioaccumulation [46-47].

Regulatory frameworks for phytopharmaceutical nanomedicines remain in a state of evolution. Agencies such as the FDA and EMA provide guidance on nanotechnology-based therapeutics, emphasizing thorough characterization, reproducibility, and safety testing. However, specific guidelines tailored to plant-derived compounds encapsulated in nanosystems are still limited, creating challenges for standardized evaluation. Parameters including particle size distribution, surface functionalization, release kinetics, and in vivo stability must be rigorously documented to satisfy regulatory requirements. Additionally, variations in natural extract composition present further hurdles, necessitating stringent quality control measures to ensure batch-to-batch consistency. Standardization of phytochemical content, purity, and bioactivity is critical for reproducible therapeutic outcomes. Addressing these challenges requires interdisciplinary collaboration among pharmacologists, toxicologists, materials scientists, and regulatory experts to develop comprehensive safety and efficacy profiles for nanocarrier-based phytomedicines, thereby facilitating clinical approval and patient trust [48-49].

8. Challenges and Limitations

Despite the significant potential of nanocarrier-mediated phytopharmacology, several challenges impede widespread clinical translation. Stability remains a primary concern, as phytochemicals are often prone to oxidation, hydrolysis, or enzymatic degradation, and their incorporation into nanocarriers does not universally mitigate these risks. Formulation reproducibility is another critical issue; variations in natural extract composition, particle size distribution, and encapsulation efficiency can lead to inconsistent therapeutic performance. Scale-up from laboratory to industrial production introduces additional complexities, requiring precise control over synthesis parameters, solvent systems, and purification methods to maintain quality and efficacy. High production costs, arising from specialized materials, multi-

step fabrication processes, and stringent quality control, may limit the commercial viability of nanopharmaceutical phytomedicines [50-51].

Patient compliance and biological variability also present challenges. Differences in skin permeability, gastrointestinal absorption, enzymatic activity, and immune response can significantly influence the pharmacokinetics and therapeutic outcomes of nanocarrier-loaded phytochemicals. Moreover, patient-specific factors such as age, disease state, and concomitant medications may affect the safety and efficacy of these formulations, necessitating personalized approaches. Addressing these limitations requires innovations in nanocarrier design, formulation standardization, and manufacturing efficiency, as well as robust clinical studies to understand interindividual variability and optimize therapeutic protocols. Overcoming these hurdles is essential to translate the promise of phytopharmaceutical nanomedicine from bench to bedside effectively [52-53].

9. Future Perspectives

The future of nanocarrier-mediated phytopharmacology is poised to benefit from advances in smart, stimuli-responsive delivery systems. These nanocarriers can respond to internal triggers, such as pH, redox potential, or enzymatic activity, or external stimuli, including light, ultrasound, or magnetic fields, to achieve on-demand release of phytochemicals at target sites. This controlled release enhances therapeutic efficacy while minimizing systemic exposure and adverse effects. Integration of artificial intelligence (AI) and predictive modeling further revolutionizes formulation design by enabling high-throughput screening, optimization of carrier composition, and individualized dosing strategies based on patient-specific parameters. Machine learning algorithms can predict the impact of nanocarrier properties on bioavailability, tissue targeting, and therapeutic outcome, facilitating rapid iteration and precision engineering [52-53].

Hybrid and multi-target nanocarriers represent another frontier, combining multiple phytochemicals or integrating natural compounds with conventional drugs for synergistic effects. Such systems can simultaneously modulate multiple signaling pathways, enhance efficacy, and reduce drug resistance. Personalized phytopharmacology is also emerging, leveraging patient-specific data—including genomics, proteomics, and metabolomics—to guide nanocarrier selection, dosing, and therapeutic strategy. Wearable or implantable delivery devices integrated with nanocarriers may allow real-time monitoring and dynamic adjustment of therapeutic release, further enhancing precision medicine approaches. Collectively, these innovations herald a future where nanotechnology, computational modeling, and phytochemistry converge to deliver safe, effective, and highly personalized natural therapeutics [54-55].

10. Conclusion

Nanotechnology has transformed the field of phytopharmacology by enabling the design of nanocarrier systems that overcome the intrinsic limitations of natural compounds, such as poor solubility, low stability, and limited bioavailability. By enhancing targeted delivery, controlled release, and systemic circulation, nanocarriers substantially improve the therapeutic efficacy

of phytochemicals while reducing off-target effects and dosing frequency. The integration of interdisciplinary approaches—combining plant science, nanotechnology, materials engineering, and pharmacology—has been instrumental in achieving these advancements. Future developments in stimuli-responsive carriers, AI-driven formulation optimization, hybrid and multi-target delivery systems, and personalized medicine are set to further revolutionize the field. Ultimately, nanocarrier-mediated phytopharmacology holds immense promise for translating natural compounds into clinically viable therapeutics, bridging traditional plant-based medicine with modern precision medicine paradigms, and delivering safe, effective, and patient-friendly therapies to diverse populations.

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