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

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Abstract:

Phytochemicals derived from natural plant sources possess remarkable therapeutic potential across oncology, inflammation, microbial infections, and neurodegenerative diseases. However, their clinical translation has been severely limited by poor aqueous solubility, rapid hepatic metabolism, chemical instability, low bioavailability, and inadequate tissue targeting. The integration of nanotechnology with phytopharmacology represents a paradigm shift in natural product-based therapeutics, offering sophisticated nanocarrier platforms—including lipid-based systems, polymeric nanoparticles, inorganic carriers, and biomimetic hybrids—to overcome these inherent limitations. Nanocarriers enhance phytochemical solubility, provide controlled and sustained release kinetics, protect bioactive molecules from enzymatic degradation, and enable both passive and active targeting to disease sites. Advanced formulations such as curcumin-loaded PLGA nanoparticles, quercetin-functionalized lipid carriers, and pH-responsive delivery systems have demonstrated markedly improved pharmacokinetic profiles, tissue-specific accumulation, and therapeutic efficacy in preclinical and clinical studies. Furthermore, multifunctional nanoplatforms enable co-delivery of multiple phytochemicals and integration of diagnostic imaging agents for theranostic applications. Despite these advances, challenges including formulation stability, batch-to-batch reproducibility, immunogenicity assessment, regulatory standardization, and cost-effective scale-up require continued attention. Future perspectives emphasize smart, stimuli-responsive nanocarriers, artificial intelligence-driven optimization, personalized phytopharmacology, and environmentally sustainable synthesis methods. Collectively, phytochemical nanomedicines represent a transformative approach to unlocking the full therapeutic potential of plant-derived compounds, bridging traditional herbal medicine with modern precision therapeutics and enabling safer, more effective, patient-centric treatment modalities.

Keywords: Phytochemicals, Nanocarriers, Nanotechnology, Bioavailability, Targeted Delivery, Polymeric Nanoparticles, Lipid-Based Carriers, Natural Products, Phytopharmacology, Nanomedicine, Theranostics, Drug Delivery, Therapeutic Efficacy.

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1. Introduction

Phytopharmacology, the study of biologically active compounds derived from plants, has long been a cornerstone of traditional medicine and modern drug discovery. Natural products have provided an abundant source of therapeutic agents, ranging from alkaloids, flavonoids, and terpenoids to polyphenols, saponins, and glycosides, many of which exhibit potent pharmacological activities such as anticancer, anti-inflammatory, antimicrobial, antioxidant, and neuroprotective effects. Historically, these plant-derived compounds have contributed significantly to the development of clinically important drugs, including paclitaxel from *Taxus brevifolia*, artemisinin from *Artemisia annua*, and vincristine from *Catharanthus roseus*. Beyond their direct therapeutic applications, phytochemicals serve as chemical scaffolds for synthetic modification, enabling the design of semi-synthetic derivatives with improved potency and selectivity [1-2]. Despite these advantages, the clinical translation of phytopharmaceuticals has been hindered by inherent physicochemical and pharmacokinetic limitations. Many natural compounds exhibit poor aqueous solubility, rapid metabolism, chemical instability, and low bioavailability, which restrict their absorption, tissue distribution, and therapeutic efficacy. Additionally, the structural complexity and stereochemical diversity of these molecules pose challenges for reproducible formulation and consistent delivery, often leading to variable clinical outcomes [3].

Conventional approaches to overcome these limitations, such as salt formation, prodrug strategies, and co-solvent systems, have shown partial success but are frequently associated with issues such as systemic toxicity, off-target effects, and short-lived therapeutic concentrations. The oral and parenteral delivery routes, while widely used, often fail to achieve optimal plasma concentrations due to first-pass metabolism, enzymatic degradation, or rapid clearance, necessitating high doses that may exacerbate adverse effects. Furthermore, the heterogeneity of plant extracts, batch-to-batch variability, and the presence of multiple active constituents complicate standardization and dosage optimization. In light of these challenges, there is a pressing need for advanced delivery strategies that can preserve the bioactivity of phytochemicals, enhance their stability, and facilitate targeted and controlled release to the desired tissue or cellular compartments [4-5].

Nanotechnology has emerged as a transformative tool to address the limitations of conventional phytopharmaceutical delivery. By engineering nanoparticles and nanocarriers with dimensions typically ranging from 1 to 200 nanometers, researchers have achieved remarkable improvements in solubility, stability, pharmacokinetics, and therapeutic efficacy of natural compounds. Nanocarriers can encapsulate hydrophobic and hydrophilic phytochemicals, protecting them from enzymatic degradation, oxidation, and premature metabolism, while enabling controlled release and sustained therapeutic action. Furthermore, the surface properties of nanocarriers, including charge, hydrophobicity, and functionalization with ligands such as antibodies, peptides, or sugars, allow for targeted delivery to specific tissues, organs, or cell types. This targeted approach reduces systemic exposure and off-target toxicity, which is particularly important for compounds with narrow therapeutic windows. Nanotechnology also enables multifunctional platforms that combine therapeutic action with

imaging or diagnostic capabilities, giving rise to theranostic systems capable of simultaneous treatment and monitoring [6-7].

Among the diverse nanocarrier systems developed for phytopharmacology, lipid-based nanocarriers (such as liposomes, solid lipid nanoparticles, and nanostructured lipid carriers) provide excellent biocompatibility and capacity to solubilize lipophilic phytochemicals. Polymeric nanoparticles, formulated from biodegradable and biocompatible polymers like PLGA, chitosan, and PEG-PLA, offer controlled release kinetics, protection from degradation, and the possibility of surface modification for active targeting. Inorganic nanoparticles, including gold, silica, and magnetic nanoparticles, not only enhance the stability and delivery of phytochemicals but also serve as platforms for imaging and external stimulus-mediated drug release. Biomimetic and hybrid systems, such as cell membrane-coated nanoparticles or lipid–polymer hybrids, further enhance circulation time, reduce immune clearance, and facilitate site-specific delivery, reflecting the growing sophistication of nanotechnology in addressing the complex challenges of phytochemical therapy [8-9].

The integration of nanotechnology with phytopharmacology is driven by the overarching goal of maximizing therapeutic efficacy while minimizing side effects. This requires a systematic understanding of the physicochemical properties of both the phytochemicals and the nanocarriers, as well as their interactions within biological systems. Factors such as particle size, surface charge, hydrophobicity, polymer composition, and encapsulation efficiency play critical roles in determining pharmacokinetics, biodistribution, and cellular uptake. Optimizing these parameters enables the development of nanomedicines capable of overcoming biological barriers such as the gastrointestinal tract, blood–brain barrier, and tumor microenvironment, which are traditionally challenging for conventional phytopharmaceuticals. Additionally, advances in surface functionalization and ligand-mediated targeting allow nanocarriers to exploit specific cellular uptake mechanisms, including receptor-mediated endocytosis and transcytosis, thereby enhancing intracellular delivery of bioactive phytochemicals [10-11].

The scope of this review encompasses a comprehensive exploration of the current state of nanotechnology-enabled phytopharmacology, emphasizing how pharmaceutical nanocarriers bridge the gap between natural compounds and clinical application. Key objectives include elucidating the types of nanocarriers suitable for phytochemicals, their mechanisms of improving solubility, stability, and targeting, and the pharmacokinetic and pharmacodynamic benefits conferred by these nanosystems. The review also aims to highlight therapeutic areas where phytochemical nanomedicines have demonstrated significant promise, such as oncology, neurodegenerative diseases, cardiovascular disorders, and infectious diseases. Furthermore, challenges associated with toxicity, biocompatibility, regulatory compliance, and large-scale production are discussed, along with emerging strategies to address these limitations. Finally, future perspectives on smart, stimuli-responsive, and personalized phytopharmaceutical nanocarriers are provided, outlining potential pathways toward clinical translation and precision medicine applications [12-13].

In conclusion, the fusion of phytopharmacology and nanotechnology represents a paradigm shift in natural product-based therapeutics. Nanocarriers offer solutions to longstanding challenges related to solubility, stability, bioavailability, and targeting of plant-derived

compounds, unlocking their full therapeutic potential. By providing controlled and targeted delivery, protecting bioactive molecules from degradation, and enabling multifunctional platforms for theranostics, nanotechnology not only enhances the efficacy of phytochemicals but also broadens their clinical applicability. As research advances, interdisciplinary collaboration among chemists, pharmacologists, materials scientists, and clinicians will be essential to translate these innovations into safe, effective, and commercially viable nanomedicines. The following sections of this review delve deeper into the types of nanocarriers, mechanisms of delivery, pharmacokinetics, therapeutic applications, and future directions, providing a roadmap for leveraging nanotechnology to maximize the impact of phytopharmacology in modern medicine [14-15].

2. Phytochemicals and Their Therapeutic Potential

Phytochemicals, naturally occurring bioactive compounds derived from plants, have garnered substantial attention in pharmacology and drug discovery due to their diverse chemical structures and wide-ranging therapeutic effects. These compounds are broadly classified into several major categories, including alkaloids, flavonoids, terpenoids, polyphenols, and saponins, each exhibiting unique physicochemical properties and bioactivities. Alkaloids, characterized by nitrogen-containing heterocyclic structures, include prominent molecules such as morphine, vincristine, and berberine. These compounds often demonstrate potent anticancer, analgesic, and antimicrobial activities, acting through mechanisms such as DNA intercalation, microtubule inhibition, enzyme modulation, and receptor targeting. Flavonoids, polyphenolic compounds found in fruits, vegetables, and medicinal herbs, exhibit strong antioxidant, anti-inflammatory, cardioprotective, and neuroprotective effects. Representative flavonoids, including quercetin, kaempferol, and epigallocatechin gallate (EGCG), modulate cellular signaling pathways, inhibit oxidative stress, and regulate inflammatory mediators, making them attractive candidates for chronic disease prevention and therapy [16-17].

Terpenoids, derived from isoprene units, encompass a vast array of structurally diverse molecules such as monoterpenes, diterpenes, and triterpenes. Compounds like paclitaxel, artemisinin, and ginsenosides exhibit anticancer, antimalarial, and immunomodulatory activities, often by interfering with cell cycle progression, angiogenesis, or pathogen metabolism. Polyphenols, including resveratrol, curcumin, and catechins, are recognized for their multifunctional pharmacological roles, such as modulation of apoptosis, inhibition of inflammatory pathways, and protection against neurodegeneration and cardiovascular disorders. Saponins, glycosidic compounds with amphiphilic properties, have demonstrated immunostimulatory, anticancer, and cholesterol-lowering effects, in addition to acting as adjuvants in vaccine formulations due to their ability to enhance antigen presentation and immune responses. These phytochemical classes collectively represent a rich pharmacopeia of structurally diverse molecules capable of targeting multiple disease pathways simultaneously, a feature often referred to as polypharmacology [18-19].

Despite their significant therapeutic potential, the clinical translation of phytochemicals faces several challenges. Most bioactive plant compounds exhibit poor aqueous solubility, which

limits their absorption and systemic bioavailability when administered orally. For example, curcumin, despite its broad spectrum of biological activities, has notoriously low solubility and rapid metabolic degradation, resulting in minimal therapeutic concentrations in target tissues. Similarly, quercetin and resveratrol undergo extensive first-pass metabolism and conjugation, producing glucuronides and sulfates that often reduce biological efficacy. Alkaloids and terpenoids, while potent, may also demonstrate cytotoxicity at high doses, narrow therapeutic windows, and off-target effects, further complicating their dosage optimization. Additionally, many phytochemicals suffer from chemical instability under physiological conditions, including susceptibility to oxidation, hydrolysis, or photodegradation, which reduces shelf-life and therapeutic reliability. Rapid clearance through renal excretion or enzymatic metabolism in the liver further diminishes the systemic residence time of these compounds, necessitating frequent dosing or higher concentrations that can trigger adverse effects [20-21].

Another critical limitation in phytochemical drug development is the heterogeneity inherent in natural extracts. The presence of multiple bioactive constituents, variable concentrations depending on plant species, harvest conditions, and extraction methods, as well as batch-to-batch variability, complicates standardization and reproducibility in clinical settings. Such variability can affect pharmacokinetics, therapeutic efficacy, and safety profiles, making regulatory approval challenging. Furthermore, many phytochemicals exhibit limited permeability across biological barriers such as the gastrointestinal epithelium, blood–brain barrier, or tumor microenvironment, restricting their effectiveness against target tissues. For example, the ability of resveratrol or quercetin to exert neuroprotective effects is often limited by poor penetration into the central nervous system, despite their potent in vitro activity. Similarly, anticancer phytochemicals may face limited intratumoral accumulation due to heterogeneous vascularization and high interstitial pressure within solid tumors [22-23].

To systematically address these challenges, recent studies have explored integrating nanotechnology with phytopharmacology to improve solubility, stability, permeability, and bioavailability. Encapsulation of phytochemicals within nanocarriers protects them from enzymatic and chemical degradation, enhances circulation time, and enables targeted delivery to specific tissues or cell types. For instance, curcumin-loaded polymeric nanoparticles or liposomes have demonstrated enhanced oral bioavailability and improved tumor targeting in preclinical models. Similarly, quercetin encapsulated in solid lipid nanoparticles or nanoemulsions shows increased stability and prolonged plasma half-life, resulting in more consistent therapeutic outcomes. Surface functionalization of nanocarriers with ligands such as folate, transferrin, or antibodies further facilitates receptor-mediated uptake, increasing intracellular concentrations in desired cell populations. This nanotechnology-driven approach not only mitigates the inherent limitations of phytochemicals but also enables controlled and sustained release, reducing the frequency of administration and minimizing systemic toxicity [24-25].

In addition to improving pharmacokinetics, nanocarriers can exploit the intrinsic polypharmacology of phytochemicals by delivering combinations of compounds in a single platform, thereby enhancing synergistic effects. For example, co-encapsulation of resveratrol and quercetin in lipid-based nanoparticles has demonstrated superior antioxidant and anti-inflammatory activity compared to individual compounds, highlighting the potential of

nanocarrier systems to preserve and potentiate natural synergy. Moreover, nanotechnology facilitates multifunctional platforms for theranostic applications, where imaging agents and bioactive phytochemicals can be co-delivered to monitor drug biodistribution, cellular uptake, and therapeutic response in real time.

3. Nanocarrier Platforms for Phytopharmacology

The integration of nanotechnology into phytopharmacology has significantly advanced the delivery, efficacy, and clinical translation of plant-derived bioactive compounds. Nanocarriers offer a versatile platform to address the intrinsic limitations of phytochemicals, including poor solubility, rapid metabolism, and limited tissue targeting, while providing controlled and sustained release. Among the diverse nanocarrier systems, lipid-based formulations have emerged as a cornerstone for improving the pharmacokinetics and therapeutic potential of phytochemicals [26]. Liposomes, spherical vesicles composed of phospholipid bilayers, can encapsulate both hydrophilic and lipophilic phytochemicals, enhancing solubility and stability. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) provide additional advantages, such as improved drug loading, protection against chemical degradation, and controlled release kinetics. SLNs utilize a solid lipid matrix to encapsulate phytochemicals, while NLCs employ a blend of solid and liquid lipids to create imperfections in the matrix that accommodate higher drug payloads. Phytosome formulations, which involve complexation of plant polyphenols or flavonoids with phospholipids, have been particularly successful in enhancing bioavailability by improving membrane permeability and facilitating efficient gastrointestinal absorption. For example, curcumin-phospholipid complexes exhibit significantly higher plasma concentrations and therapeutic effects than free curcumin, highlighting the capacity of lipid-based carriers to overcome poor solubility and first-pass metabolism. These lipid platforms also allow surface functionalization with targeting ligands, enabling receptor-mediated delivery to specific tissues or cell types, including tumor cells, inflammatory sites, and the central nervous system [27-28].

Polymeric nanoparticles represent another highly versatile class of nanocarriers for phytopharmacology. These systems are often constructed from biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, polycaprolactone (PCL), and PEGylated derivatives. Polymeric nanoparticles enable precise control over particle size, surface charge, and degradation kinetics, which directly influence drug release profiles and tissue distribution. By encapsulating phytochemicals within a polymeric matrix, these carriers protect sensitive bioactives from enzymatic degradation, extend circulation half-life, and facilitate sustained release over hours or days. Surface modification strategies, such as PEGylation, folate conjugation, or antibody functionalization, enhance cellular uptake and targeting efficiency, particularly for cancer therapy and neuroprotective applications. Chitosan-based nanoparticles, with their intrinsic mucoadhesive properties, have shown enhanced gastrointestinal absorption of orally administered phytochemicals like quercetin and berberine, while PLGA nanoparticles have been widely investigated for delivering hydrophobic plant compounds such as paclitaxel and curcumin in oncology. Additionally, polymeric nanoparticles allow co-delivery of multiple phytochemicals or combination therapies, enabling synergistic pharmacological effects and reducing the likelihood of drug resistance [29-30].

Inorganic nanocarriers, including gold, silica, and magnetic nanoparticles, offer unique opportunities for phytopharmaceutical delivery, particularly in theranostic applications where diagnosis and therapy are combined. Gold nanoparticles (AuNPs) can be conjugated with phytochemicals to enhance cellular uptake, enable photothermal therapy, and provide real-time imaging capabilities due to their tunable surface plasmon resonance. Silica nanoparticles, especially mesoporous silica, provide a high surface area for drug loading and can be functionalized with stimuli-responsive gates that release phytochemicals in response to pH, enzymes, or redox conditions. Magnetic nanoparticles enable external guidance and targeted accumulation in desired tissues under a magnetic field, improving therapeutic efficacy while minimizing systemic exposure. These inorganic carriers also allow co-delivery of imaging agents and phytochemicals, enabling simultaneous monitoring of biodistribution and therapeutic response. For instance, magnetic silica nanoparticles loaded with curcumin or quercetin have demonstrated enhanced anticancer efficacy and imaging capability in preclinical models, showcasing the potential of inorganic nanocarriers in precision phytotherapy [31-32].

Hybrid and biomimetic systems represent the next frontier in phytopharmaceutical nanocarrier design, combining the advantages of multiple platforms to overcome individual limitations. Lipid–polymer hybrid nanoparticles integrate the stability and controlled release properties of polymers with the biocompatibility and membrane fusion capability of lipids, resulting in improved circulation time, drug loading, and tissue targeting. Cell membrane-coated nanoparticles, derived from erythrocytes, platelets, or cancer cells, provide immune evasion capabilities by presenting “self” markers, thereby prolonging systemic circulation and reducing clearance by the reticuloendothelial system. Exosome-mimetic carriers, engineered to replicate the natural vesicular transport mechanisms of endogenous exosomes, offer enhanced cellular uptake, organ-specific targeting, and minimal immunogenicity. Such biomimetic platforms are particularly valuable for delivering sensitive phytochemicals like siRNA-conjugated polyphenols, anti-inflammatory alkaloids, or neuroprotective terpenoids, which require precise intracellular delivery. By tailoring the composition, surface functionality, and size of hybrid carriers, researchers can achieve controlled release profiles, targeted tissue deposition, and synergistic therapeutic effects, addressing both pharmacokinetic and pharmacodynamic challenges of phytochemicals [33-34].

The choice of nanocarrier depends on the specific phytochemical, therapeutic goal, and route of administration. Lipid-based systems are preferred for enhancing solubility and gastrointestinal absorption; polymeric carriers excel in sustained release and targeted delivery; inorganic nanoparticles offer theranostic potential; and hybrid/biomimetic platforms provide immune evasion, multifunctionality, and advanced targeting capabilities. Table 2 summarizes the key nanocarrier types, their mechanisms, and applications in phytopharmaceutical delivery. This comparative analysis highlights the advantages and limitations of each platform, guiding rational selection based on physicochemical properties, desired pharmacokinetics, and clinical objectives.

Overall, the convergence of nanotechnology with phytopharmacology has created a transformative approach to plant-based therapeutics. By leveraging the structural versatility, surface functionalization, and controlled release capabilities of various nanocarriers,

researchers can overcome the traditional limitations of phytochemicals, enhance bioavailability, improve targeting specificity, and reduce systemic toxicity. Such advancements not only facilitate the clinical translation of natural compounds but also enable the development of multifunctional, personalized, and theranostic platforms for a wide range of diseases, including cancer, neurodegeneration, infectious diseases, and metabolic disorders. The continued exploration and optimization of lipid-based, polymeric, inorganic, and hybrid nanocarriers promise to unlock the full therapeutic potential of phytochemicals, bridging the gap between natural product pharmacology and advanced nanomedicine [35-36].

4. Mechanisms of Nanocarrier-Mediated Phytochemical Delivery

The integration of nanocarriers into phytopharmacology has revolutionized the delivery mechanisms of plant-derived bioactive compounds, fundamentally improving solubility, absorption, bioavailability, and therapeutic efficacy. Many phytochemicals, such as curcumin, quercetin, resveratrol, and berberine, suffer from poor aqueous solubility and rapid systemic clearance, limiting their clinical potential. Nanocarriers enhance solubility by encapsulating hydrophobic phytochemicals within lipid bilayers, polymeric matrices, or mesoporous inorganic frameworks, thereby creating microenvironments that allow effective dissolution and transport across biological membranes. Lipid-based carriers, such as liposomes, transfersomes, and phytosomes, exploit their amphiphilic structure to incorporate hydrophobic phytochemicals within their hydrophobic core while maintaining a hydrophilic exterior that ensures dispersion in aqueous biological media. This structural design not only improves solubility but also facilitates passive diffusion through cell membranes, enhancing cellular uptake and systemic bioavailability. Moreover, surfactant-rich nanosystems such as ethosomes and niosomes utilize ethanol or non-ionic surfactants to fluidize lipid bilayers and increase transdermal or mucosal penetration, thereby overcoming one of the major barriers in phytochemical delivery [37-38].

Controlled and sustained release is another central mechanism that defines the therapeutic advantages of nanocarriers in phytopharmacology. Polymeric nanoparticles, particularly those constructed from biodegradable polymers like PLGA, chitosan, and PCL, provide a matrix for gradual release of encapsulated phytochemicals through polymer degradation. The degradation kinetics can be tailored by modulating polymer composition, molecular weight, and copolymer ratios, enabling precise control over drug release rates that align with desired pharmacokinetic profiles. Lipid-based systems, in contrast, regulate release through diffusion mechanisms, where the phytochemical gradually partitions out of the lipid matrix into surrounding biological fluids. Hybrid systems that combine lipid and polymer matrices allow synergistic control, where diffusion and degradation processes can be fine-tuned to achieve prolonged therapeutic windows while minimizing peak plasma concentrations that may lead to toxicity. For example, curcumin-loaded PLGA–lipid hybrid nanoparticles demonstrate a biphasic release pattern: an initial moderate burst to achieve therapeutic concentrations, followed by sustained release over 24–72 hours to maintain efficacy, illustrating the importance of nanocarrier architecture in pharmacokinetic modulation [39-40].

Targeted delivery represents a critical advantage of nanocarrier-mediated phytochemical transport. Nanocarriers can exploit both passive and active targeting mechanisms to selectively accumulate in desired tissues or cellular compartments. Passive targeting relies on the enhanced permeability and retention (EPR) effect observed in tumors or inflamed tissues, where nanoscale carriers extravasate through leaky vasculature and accumulate due to poor lymphatic drainage. Lipid- and polymer-based nanoparticles loaded with anticancer phytochemicals, such as paclitaxel–curcumin co-loaded systems, have demonstrated preferential tumor localization through EPR, enhancing cytotoxic efficacy while sparing healthy tissues. Active targeting strategies further improve selectivity through surface functionalization with ligands such as antibodies, aptamers, folic acid, or peptides that recognize specific receptors on target cells. For instance, folate-decorated PLGA nanoparticles carrying quercetin preferentially bind to folate receptor-overexpressing cancer cells, triggering receptor-mediated endocytosis and intracellular release. Such targeting not only increases therapeutic index but also reduces systemic exposure, minimizing off-target side effects—a critical consideration for phytochemicals with narrow therapeutic windows [41-42].

Nanocarriers also provide protection from enzymatic degradation and metabolic clearance, which is a major limitation for many plant-derived compounds. Phytochemicals are often susceptible to oxidation, hydrolysis, or first-pass metabolism, which dramatically reduces their bioavailability. Encapsulation within lipid, polymeric, or inorganic carriers shields these molecules from harsh physiological conditions, enzymatic hydrolysis, and pH fluctuations. Polymeric nanoparticles, for example, create a physical barrier that prevents rapid degradation by esterases or cytochrome P450 enzymes, while lipid-based carriers can evade metabolic enzymes in the gastrointestinal tract, allowing oral phytochemicals like berberine and curcumin to achieve higher plasma concentrations. Inorganic carriers, such as silica or gold nanoparticles, offer additional protection through their rigid structures, and when functionalized with biocompatible coatings like PEG or chitosan, they can further reduce recognition and clearance by the reticuloendothelial system (RES), prolonging circulation time and enhancing tissue accumulation. Hybrid systems combine these protective features with targeting strategies, resulting in multifunctional delivery platforms capable of sustained release, site-specific accumulation, and metabolic stabilization [43-44].

Cellular uptake of nanocarrier-encapsulated phytochemicals is facilitated by multiple mechanisms, including endocytosis, phagocytosis, macropinocytosis, and membrane fusion. Particle size, shape, surface charge, and elasticity significantly influence the internalization pathways. Nanoparticles in the range of 50–200 nm are efficiently internalized by most mammalian cells, while surface charge modulation can favor interaction with negatively charged cell membranes. For instance, cationic chitosan nanoparticles enhance cellular uptake due to electrostatic attraction with anionic phospholipids, whereas neutral or PEGylated nanoparticles exhibit prolonged systemic circulation and reduced non-specific cellular uptake. Targeting ligands further direct the nanocarriers to specific receptor-mediated pathways, ensuring that the phytochemical payload is delivered directly to the intracellular site of action. Once internalized, nanocarriers release the encapsulated phytochemicals in a controlled manner, influenced by the intracellular environment, pH gradients, or enzymatic activity, thereby optimizing therapeutic efficacy while minimizing cytotoxicity [45-46].

In addition to cellular-level mechanisms, nanocarriers influence systemic pharmacokinetics by modulating absorption, distribution, metabolism, and excretion (ADME) of phytochemicals. Oral delivery of nanoparticle-encapsulated compounds benefits from enhanced solubility and protection from gastrointestinal degradation, resulting in higher absorption and plasma exposure. Intravenous or topical administration leverages surface modifications to evade RES clearance and improve targeted tissue accumulation. Nanocarrier architecture, including hydrophilic coatings, ligand functionalization, and particle rigidity, can be systematically optimized using predictive modeling to achieve desired pharmacokinetic profiles. Preclinical studies have demonstrated that nanoencapsulation of flavonoids, terpenoids, and alkaloids significantly increases bioavailability, prolongs half-life, and reduces systemic toxicity, highlighting the translational potential of nanocarrier-mediated phytochemical delivery [47].

Overall, the mechanisms of nanocarrier-mediated phytochemical delivery encompass a multifaceted strategy that combines enhanced solubility, controlled release, targeted tissue accumulation, protection from metabolic degradation, and optimized cellular uptake. By tailoring the physicochemical properties of nanocarriers and integrating lipidic, polymeric, inorganic, or hybrid systems, researchers can overcome the inherent limitations of conventional phytopharmaceuticals and achieve improved pharmacokinetics, pharmacodynamics, and therapeutic efficacy. This mechanistic understanding forms the foundation for rational design and clinical translation of next-generation phytochemical-based nanomedicines. Table 3 summarizes the primary mechanisms, nanocarrier types, and examples of phytochemicals delivered through these strategies, providing a comprehensive overview of how nanotechnology is bridging natural compounds with modern pharmaceutical science [48].

5. Pharmacokinetics, Biodistribution, and Bioavailability

The pharmacokinetics, biodistribution, and bioavailability of phytochemicals are profoundly influenced by the physicochemical properties of their nanocarrier delivery systems. Many plant-derived compounds, including polyphenols, flavonoids, alkaloids, and terpenoids, face intrinsic limitations in clinical application due to low aqueous solubility, poor membrane permeability, rapid metabolic degradation, and systemic clearance. Nanocarriers such as lipid-based nanoparticles, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and inorganic or hybrid systems have emerged as transformative platforms that overcome these barriers, enabling controlled, targeted, and sustained delivery of phytochemicals. One of the primary determinants of pharmacokinetic behavior is particle size, which governs systemic circulation, tissue penetration, and cellular uptake. Nanocarriers in the 50–200 nm range often exhibit enhanced permeability and retention (EPR) effects in tumor or inflamed tissues, allowing passive accumulation and prolonged tissue residency. Smaller nanoparticles may facilitate renal clearance, whereas larger particles risk uptake by the reticuloendothelial system (RES), influencing biodistribution profiles [49-50]. Surface charge similarly plays a pivotal role: neutral or slightly negative nanoparticles typically evade rapid clearance by phagocytic cells, whereas positively charged particles exhibit improved cellular internalization due to electrostatic interactions with negatively charged cell membranes but may be rapidly recognized and cleared by immune cells if not properly shielded. Hydrophilic surface coatings, such as polyethylene glycol (PEG), provide a steric barrier against

opsonization, enhancing systemic circulation time and improving the likelihood of reaching target tissues.

The composition of nanocarriers—including lipid matrix, polymer type, or inorganic core—also directly impacts pharmacokinetics and tissue distribution. Lipid-based carriers provide a biocompatible matrix that enhances solubility of hydrophobic phytochemicals and facilitates transcellular and paracellular transport across biological membranes. Polymeric nanoparticles, particularly those made from biodegradable polymers like PLGA or chitosan, allow controlled release by slow polymer degradation, which contributes to prolonged plasma half-life and reduced fluctuation in drug concentration [51-52]. Hybrid systems combining lipids and polymers merge the advantages of both platforms, offering a tunable balance between release kinetics and biodistribution. Inorganic nanocarriers such as silica, gold, or iron oxide particles provide structural rigidity and can be functionalized with targeting ligands, enabling precise localization and imaging capabilities, although their biodegradability and long-term safety must be carefully considered. The physicochemical tuning of these carriers enables modulation of absorption, distribution, metabolism, and excretion (ADME) parameters to optimize therapeutic efficacy.

Pharmacokinetic studies of phytochemical-loaded nanocarriers reveal significant improvements in systemic circulation, tissue accumulation, and bioavailability compared to free compounds. For instance, curcumin encapsulated in PLGA nanoparticles demonstrates a marked increase in plasma half-life, reduced metabolic clearance, and enhanced accumulation in target tissues such as the liver and tumor sites. Similarly, quercetin-loaded lipid nanoparticles show higher oral bioavailability by protecting the compound from enzymatic degradation and facilitating transcellular transport in the gastrointestinal tract. Nanoencapsulation of resveratrol and berberine has resulted in improved pharmacokinetic profiles, with prolonged circulation times, higher peak plasma concentrations, and enhanced tissue-specific accumulation, illustrating the generalizable advantages of nanocarrier strategies for phytochemicals. The size, surface chemistry, and material composition of the nanocarrier are critical determinants of these outcomes, and careful design is necessary to balance circulation, uptake, and clearance [53-54].

Biodistribution patterns are often shaped by the interplay between passive targeting, active targeting, and nanocarrier physicochemistry. Passive targeting exploits the EPR effect in tumors, inflamed tissues, or areas with compromised vasculature, while active targeting involves the functionalization of nanocarrier surfaces with ligands such as folic acid, antibodies, peptides, or aptamers that bind specific receptors on target cells. For example, folate-conjugated polymeric nanoparticles carrying anticancer phytochemicals preferentially accumulate in folate receptor-overexpressing tumors, enhancing local drug concentrations while minimizing systemic exposure. Similarly, mannose-functionalized nanoparticles loaded with immunomodulatory phytochemicals target macrophages and dendritic cells in the lymphoid tissues, improving immune response modulation. Hybrid targeting strategies, where passive accumulation is combined with ligand-mediated cellular uptake, have demonstrated superior tissue-specific delivery and therapeutic outcomes in preclinical models [55-56].

In vitro–in vivo correlation (IVIVC) studies underscore the translational potential of nanocarrier-mediated phytochemical delivery. In vitro assays assessing release kinetics, solubility enhancement, and cellular uptake are often predictive of in vivo behavior, provided that nanocarrier properties are carefully characterized. For example, curcumin-loaded SLNs show sustained release in vitro, which translates into prolonged plasma levels and enhanced tumor accumulation in rodent models. Similarly, chitosan-based nanoparticles demonstrate enhanced mucosal adhesion and absorption in vitro, which is reflected in increased systemic bioavailability upon oral administration. Such IVIVC analyses are essential for rational design and optimization of phytochemical nanomedicines, as they allow prediction of pharmacokinetic outcomes and adjustment of formulation parameters before extensive in vivo testing.

Nanocarriers also improve bioavailability by protecting phytochemicals from first-pass metabolism, enzymatic degradation, and chemical instability. Many polyphenols and alkaloids undergo extensive hepatic metabolism when administered orally, resulting in low systemic exposure and reduced efficacy. Encapsulation within nanoparticles shields these compounds during gastrointestinal transit and facilitates absorption through transcellular pathways, effectively bypassing or mitigating first-pass metabolism. Additionally, surface-functionalized nanoparticles can interact with intestinal transporters or mucosal surfaces to further enhance uptake, increasing the fraction of active compound reaching systemic circulation. Controlled release from the nanocarrier ensures maintenance of therapeutic concentrations over extended periods, reducing the frequency of dosing and improving patient compliance [57-58].

Overall, the pharmacokinetics, biodistribution, and bioavailability of phytochemicals are significantly enhanced through rational design of nanocarrier systems. By modulating size, surface charge, composition, and targeting ligands, nanocarriers overcome the intrinsic limitations of conventional phytopharmaceuticals, facilitating controlled release, tissue-specific accumulation, and prolonged systemic exposure. Such improvements translate into enhanced efficacy, reduced toxicity, and broader clinical applicability. Table 3 provides a comparative summary of selected phytochemicals, their corresponding nanocarriers, and pharmacokinetic enhancements, highlighting the transformative impact of nanotechnology on phytopharmacology and establishing a foundation for the development of next-generation plant-based nanomedicines [59-60].

6. Therapeutic Applications

The therapeutic potential of phytochemicals is vast, encompassing anticancer, anti-inflammatory, antimicrobial, antiviral, neuroprotective, and cardioprotective activities. However, the clinical translation of these natural compounds has long been limited by poor aqueous solubility, low chemical stability, rapid metabolic clearance, and inadequate tissue targeting. Nanocarrier-based delivery systems have emerged as an effective strategy to overcome these limitations, enhancing the therapeutic efficacy, bioavailability, and targeted delivery of phytochemicals across a wide range of disease contexts. One of the most extensively explored applications is in oncology, where

anticancer phytochemicals such as curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), and genistein have shown significant potential. Nanoparticles, including lipid-based carriers, polymeric systems, and hybrid nanostructures, facilitate selective tumor targeting by leveraging the enhanced permeability and retention (EPR) effect, which enables preferential accumulation in tumor tissues due to leaky vasculature and poor lymphatic drainage. Furthermore, active targeting strategies, such as ligand-functionalized nanoparticles, allow binding to tumor-specific receptors, enhancing cellular uptake while minimizing off-target toxicity. Curcumin-loaded PLGA nanoparticles, for instance, have demonstrated improved cytotoxicity against various cancer cell lines, enhanced apoptosis induction, and reduced systemic toxicity compared to free curcumin. Similarly, resveratrol encapsulated in lipid-based nanocarriers exhibits prolonged circulation time, enhanced tumor accumulation, and superior antitumor activity in vivo, highlighting the synergistic benefits of nanotechnology in augmenting the pharmacodynamic effects of phytochemicals [61-62].

Beyond cancer therapy, phytochemical-loaded nanocarriers have shown remarkable efficacy in modulating inflammation and oxidative stress. Chronic inflammatory conditions, such as arthritis, inflammatory bowel disease, and neuroinflammation, are characterized by elevated levels of pro-inflammatory cytokines and reactive oxygen species (ROS). Phytochemicals like quercetin, luteolin, curcumin, and boswellic acids possess potent anti-inflammatory and antioxidant properties but often fail to achieve therapeutic concentrations in target tissues due to rapid metabolism and poor permeability. Nanocarrier platforms—including polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, and phytosomes—enhance the solubility and stability of these compounds, enabling controlled and sustained release while protecting them from enzymatic degradation. For example, curcumin-loaded SLNs and NLCs have been shown to reduce pro-inflammatory markers in animal models of arthritis and colitis, while quercetin encapsulated in PLGA nanoparticles mitigates oxidative stress and modulates inflammatory signaling pathways. The targeted delivery of these nanoformulations to inflamed tissues further increases local drug concentration, improves therapeutic efficacy, and reduces systemic side effects, illustrating the potential of nanocarrier-assisted phytochemicals in managing chronic inflammatory diseases [63-64].

Nanotechnology has also revolutionized the antimicrobial and antiviral applications of phytochemicals. Plant-derived compounds such as berberine, eugenol, allicin, and tea tree oil possess broad-spectrum antibacterial, antifungal, and antiviral activities but are often limited by poor solubility, volatility, and rapid degradation. Encapsulation within nanocarriers enhances solubility, protects the active compounds from premature inactivation, and allows for controlled release at the site of infection. Lipid-based nanoparticles, polymeric nanospheres, and hybrid carriers have been employed to improve the therapeutic index of these compounds. For instance, berberine-loaded chitosan nanoparticles demonstrate enhanced cellular uptake and antimicrobial efficacy against multidrug-resistant bacterial strains, while curcumin and quercetin nanoformulations have shown antiviral activity against influenza and other enveloped viruses. Moreover, nanocarriers can facilitate the delivery of phytochemicals across mucosal barriers, improving bioavailability for oral, nasal, and pulmonary

administration. The ability to co-encapsulate multiple phytochemicals or combine them with conventional antibiotics or antivirals further expands their therapeutic potential, offering a promising strategy to combat drug-resistant infections and emerging viral threats [65-66].

Neuroprotective and cardioprotective effects of phytochemicals have also been significantly enhanced through nanocarrier-mediated delivery. Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and stroke are associated with oxidative stress, inflammation, and protein aggregation in the central nervous system (CNS). Phytochemicals like curcumin, resveratrol, EGCG, and ginsenosides possess neuroprotective properties but exhibit poor blood–brain barrier (BBB) penetration and rapid systemic clearance. Nanocarrier systems, including polymeric nanoparticles, solid lipid nanoparticles, and lipid–polymer hybrids, have been engineered to traverse the BBB via receptor-mediated transcytosis or adsorptive-mediated transport, delivering phytochemicals directly to neuronal tissues. For example, curcumin-loaded PLGA nanoparticles conjugated with transferrin or lactoferrin have demonstrated enhanced BBB penetration and improved cognitive function in animal models of Alzheimer's disease [67-68]. Similarly, resveratrol and quercetin nanoformulations have shown efficacy in reducing oxidative stress, inhibiting amyloid-β aggregation, and modulating neuroinflammatory pathways. In cardiovascular applications, phytochemicals such as resveratrol, quercetin, and curcumin-loaded nanocarriers improve endothelial function, reduce oxidative stress, and prevent atherosclerotic plaque formation by enhancing systemic bioavailability and targeted delivery to cardiac tissues. Nanocarrier-mediated delivery enables sustained release, protecting cardiovascular tissues from repeated oxidative insults and maximizing therapeutic efficacy with minimal systemic toxicity [69-70].

The versatility of nanocarrier platforms allows fine-tuning of drug release kinetics, tissue targeting, and pharmacokinetics, which is critical for optimizing the therapeutic effects of phytochemicals across different disease contexts. By adjusting particle size, surface charge, composition, and functionalization, nanocarriers can achieve site-specific delivery, controlled release, and protection against premature metabolism. Passive targeting through size-mediated accumulation and active targeting via receptor-ligand interactions collectively enhance tissue specificity and therapeutic outcomes. Furthermore, hybrid nanocarrier systems combining lipids, polymers, and inorganic materials can simultaneously address solubility, stability, and targeting challenges while providing additional functionalities such as imaging or theranostic potential. The integration of nanotechnology with phytopharmacology has thus transformed the clinical potential of natural compounds, overcoming long-standing limitations and enabling their application in diverse therapeutic areas.

In summary, nanocarrier-mediated delivery of phytochemicals provides a powerful platform to enhance anticancer, anti-inflammatory, antimicrobial, neuroprotective, and cardioprotective activities. By improving solubility, stability, tissue targeting, and bioavailability, these nanoformulations maximize therapeutic efficacy while minimizing systemic side effects. Table 2 summarizes representative nanocarriers used for phytochemical delivery, highlighting their composition, targeted applications, and the resulting enhancements in pharmacokinetics, biodistribution, and therapeutic

activity. The convergence of nanotechnology and phytopharmacology thus offers a promising pathway for the development of next-generation natural product-based therapeutics, bridging the gap between traditional herbal medicine and modern precision nanomedicine [71-72].

7. Safety, Toxicity, and Regulatory Considerations

While the integration of nanotechnology with phytopharmacology has substantially enhanced therapeutic efficacy, safety and biocompatibility remain paramount concerns. Phytochemical-loaded nanocarriers must undergo rigorous evaluation to ensure cytocompatibility, minimal hemolytic activity, and low immunogenicity. Biodegradable polymers, lipid-based carriers, and hybrid nanoparticles are generally well-tolerated; however, surface functionalization, particle size, and the nature of the encapsulated phytochemicals can influence cellular uptake and cytotoxicity profiles [73-74]. In vitro studies, including MTT, LDH release, and apoptosis assays, provide initial insights into cytotoxic effects on relevant cell lines, whereas in vivo studies evaluate biodistribution, systemic toxicity, and potential organ-specific accumulation. Immunogenicity, particularly for lipid- or protein-coated nanocarriers, requires careful assessment due to the possibility of triggering unwanted immune responses or inflammation [75-76]. Long-term safety studies are critical, as repeated administration may lead to accumulation or unforeseen biological interactions. Environmental safety is another emerging consideration, as nanocarriers released into ecosystems could interact with non-target organisms. Regulatory pathways for phytopharmaceutical nanomedicines present unique challenges because these formulations combine natural compounds with engineered nanomaterials. Regulatory agencies such as the FDA and EMA provide frameworks for conventional pharmaceuticals and biologics but have limited specific guidance for nano-enabled plant-based therapeutics [77-78]. Detailed characterization of nanocarrier composition, pharmacokinetics, toxicity, and stability is essential to satisfy regulatory requirements. Moreover, standardization of natural extracts is critical to minimize batch-to-batch variability, ensuring reproducibility and safety. Collectively, comprehensive toxicological evaluation and regulatory compliance are essential to translate phytochemical nanomedicines from bench to bedside, balancing innovation with patient safety [79-80].

8. Challenges and Limitations

Despite their promise, phytochemical nanomedicines face several critical challenges that must be addressed for successful clinical translation. Stability is a primary concern; many natural compounds are chemically labile, prone to oxidation, hydrolysis, or photodegradation, which may compromise efficacy during storage and use. Nanocarrier formulations must therefore maintain physical and chemical stability under variable temperature, humidity, and pH conditions. Reproducibility of nanoparticle synthesis and encapsulation efficiency is another challenge, particularly when dealing with complex plant extracts containing multiple bioactive constituents. Scale-up from laboratory to industrial production often introduces variability in particle size distribution, surface charge, and drug loading, which can impact bioavailability and therapeutic outcomes. The inherent complexity of natural extracts further complicates standardization, as minor variations in phytochemical composition can significantly

alter pharmacological effects [81-82]. High production costs for nanocarrier-based phytomedicines also present limitations, stemming from expensive raw materials, complex fabrication methods, and stringent quality control measures. Patient compliance and variability in biological response are additional challenges; differences in skin permeability, gastrointestinal absorption, or enzymatic metabolism can affect the pharmacokinetics and pharmacodynamics of nanocarrier-encapsulated phytochemicals. Furthermore, regulatory gaps and lack of standardized guidelines for phytopharmaceutical nanomedicines introduce uncertainty for developers, potentially slowing translation to clinical use. Addressing these limitations requires interdisciplinary approaches combining chemistry, materials science, pharmacology, and regulatory expertise to optimize formulations and ensure consistent, safe, and cost-effective therapeutic outcomes [83-84].

9. Future Perspectives

The future of phytopharmacology in the nanotechnology era is poised for transformative advancements through smart, stimuli-responsive, and personalized delivery systems. Emerging nanocarriers capable of responding to environmental triggers—such as pH, temperature, enzymatic activity, or light—enable on-demand release of phytochemicals at target sites, improving therapeutic efficacy while minimizing systemic exposure. Integration with artificial intelligence (AI) and predictive modeling offers new avenues for formulation optimization, enabling rapid screening of polymer matrices, lipid compositions, and ligand modifications to achieve maximum bioavailability and targeted delivery [85-86]. Hybrid and multi-target nanocarriers, which combine several phytochemicals within a single system, can address complex disease mechanisms such as cancer, inflammation, or neurodegeneration, allowing synergistic therapeutic effects. Personalized phytopharmacology represents another exciting frontier, where patient-specific factors such as metabolic profile, genetic background, and disease state inform tailored nanocarrier design for optimized dosing and delivery. Additionally, convergence with wearable devices and real-time monitoring systems may allow dynamic tracking of phytochemical release, pharmacokinetics, and therapeutic response, ushering in precision herbal nanomedicine. Environmental sustainability and green synthesis approaches, including plant-mediated nanoparticle fabrication, further expand the potential for eco-friendly, scalable production. Overall, the integration of nanotechnology, AI, and patient-centered design promises to redefine the clinical application of phytochemicals, bridging traditional herbal medicine with modern precision therapeutics [87-88].

10. Conclusion

Nanotechnology has unlocked new dimensions in phytopharmacology, enabling the delivery of plant-derived bioactive compounds with improved solubility, stability, bioavailability, and tissue-specific targeting. Through lipid-based, polymeric, inorganic, and hybrid nanocarriers, phytochemicals can achieve controlled and sustained release, enhanced cellular uptake, and protection from enzymatic and metabolic degradation, thereby overcoming longstanding limitations of conventional formulations. The therapeutic applications of these nanocarrier systems span oncology, inflammation, infectious diseases, neuroprotection, and

cardioprotection, demonstrating significant potential for improving patient outcomes while minimizing systemic toxicity. Safety, regulatory, and manufacturing challenges remain, emphasizing the need for rigorous biocompatibility testing, standardized extract characterization, and scalable production methods. Looking forward, smart, stimuli-responsive, AI-optimized, and personalized phytopharmaceutical nanocarriers offer unprecedented opportunities to harness the full therapeutic potential of natural compounds. Interdisciplinary collaboration between plant science, nanotechnology, pharmacology, and regulatory sciences will be crucial for translating these innovations into clinically viable, next-generation nanomedicines, ultimately bridging the gap between traditional herbal remedies and modern precision therapeutics.

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