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SYSTEMATIC REVIEW ON NANOTECHNOLOGY FOR PHYTO MEDICINE RESEARCH AND DRUG DEVELOPMENT.

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Abstract :

The combination of plant-derived bioactives and nanotechnology, known as "nano-phytomedicine," has shown promise in overcoming the intrinsic drawbacks of traditional phytochemicals, such as their poor solubility, low bioavailability, and restricted tissue targeting. Recent developments in nanocarrier systems, including as polymeric nanoparticles, lipid-based carriers, nanoemulsions, SNEDDS, and green-synthesized nanoparticles, are highlighted in this systematic review along with how they can improve pharmacokinetics, efficacy, and safety. Improved results in preclinical and early clinical investigations are presented for disease-oriented applications in cancer, neurological, metabolic, and infectious illnesses. Along with new possibilities in AI-guided nanoformulation design, individualized phytomedicine, and interaction with conventional medical systems, the main obstacles in toxicity, regulatory approval, clinical translation, and standardization are examined. All things considered, nano-phytomedicine presents a revolutionary strategy by fusing cutting-edge nanotechnology with conventional therapies to provide safe, focused, and patient-centered treatments.

Keywords: Nano-phytomedicine; phytochemical delivery systems,Bioavailability, Bioactivity, Nanotechnology, Phytomedicine.

1. Introduction

For centuries, phytomedicines—which are made from plant-based bioactive compounds—have been used to prevent and treat a wide range of illnesses. They have a variety of therapeutic effects, such as anti-inflammatory, antioxidant, anticancer, neuroprotective, and antimicrobial properties (Patwardhan et al., 2005; Li et al., 2016). Many phytochemicals have enormous promise, but their medicinal efficacy is generally restricted by their poor aqueous solubility, low oral bioavailability, fast metabolism, and instability under physiological conditions (Anand et al., 2010).

In order to get around these restrictions, nanotechnology has become a potent tool that makes it possible to create complex nanocarrier systems that improve pharmacokinetic profiles, protect bioactive compounds from degradation, increase solubility, and enable targeted or controlled release at the site of action (Patra et al., 2018; Sanna et al., 2014). With better efficacy and fewer side effects, nanophytomedicine, which combines these nanocarrier techniques with plant-derived medicines, has the potential to bridge the gap between conventional medicine and contemporary drug delivery.

Polymeric nanoparticles, lipid-based carriers, nanoemulsions, self-nanoemulsifying systems, and green-synthesized nanoparticles have been shown in recent studies to improve the delivery and therapeutic results of bioactives like curcumin, resveratrol, quercetin, and paclitaxel in a variety of disease models, including cancer, neurodegenerative disorders, metabolic syndrome, and infectious diseases (Yallapu et al., 2012; Mohanty et al., 2018).

The potential and difficulties of nano-phytomedicines in contemporary drug development are highlighted in this review, which offers a methodical and thorough overview of the field. It focuses on the most recent developments in nanocarrier design, disease-oriented applications, pharmacokinetics, safety, clinical translation, and emerging trends like AI-guided formulation, personalized therapy, and integration with traditional medicine systems.

Furthermore, the combination of modern technologies like machine learning and artificial intelligence (AI) with nanophytomedicines is creating new opportunities for individualized therapy, optimization, and rational design. AI-driven methods can forecast patient-specific dosing schedules, drug–excipient interactions, and ideal nanocarrier compositions, speeding up formulation development and enhancing therapeutic results. Additionally, integrating nano-

phytomedicines with conventional medical systems presents a special chance to maximize the synergistic effects of several bioactives while guaranteeing accurate, targeted administration. In addition to improving phytochemicals' medicinal potential, these multidisciplinary approaches open the door for the development of novel, secure, and efficient plant-based treatments.

2. Methodology (PRISMA-Based Systematic Review)

2.1 Search Strategy and Data Sources

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a comprehensive and methodical literature search was conducted to locate relevant studies on the application of nanotechnology in phytomedicine research and drug development (Moher et al., 2009; Page et al., 2021). Major electronic databases like PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar were searched to ensure comprehensive coverage of biological, pharmacological, and nanotechnology literature. Medical Subject Headings (MeSH) and free-text keywords employing Boolean operators were combined in the search strategy, such as "phytomedicine" OR "phytochemicals" OR "plant-derived compounds" AND "nanotechnology" OR "nanocarriers" OR "nanoparticles" AND "drug delivery" OR "drug development." To reflect contemporary developments and translational trends in nano-enabled phytomedicine, English-language studies published between 2010 and 2024 were taken into consideration. In order to reduce publication bias and improve the review's completeness, the reference lists of chosen articles and pertinent reviews were also manually screened to find any potentially eligible studies that were missed in the first database search (Liberati et al., 2009; Siddaway et al., 2019).

2.2 Inclusion and Exclusion Criteria

To guarantee relevance, quality, and compatibility with the goals of this systematic review, studies were chosen using predetermined inclusion and exclusion criteria. Original research publications and systematic reviews discussing the use of nanotechnology-based phytomedicine delivery systems in the context of medication development were included. In vitro, in vivo, and clinical studies that examined nanoformulated plant-derived bioactive chemicals employing well-characterized nanocarrier systems, such as polymeric nanoparticles,

lipid-based nanocarriers, nanoemulsions, and green-synthesized nanoparticles, were eligible study designs. According to Patra et al. (2018) and Bonifácio et al. (2014), studies have to explicitly identify the phytochemical or plant extract, define the type of nanocarrier and formulation approach, and provide pertinent pharmacological, pharmacokinetic, or therapeutic outcomes.

Studies that did not include a nanotechnological component, concentrated only on traditional herbal formulations, or lacked enough formulation or biological evaluation data were excluded. To preserve scientific rigor and repeatability, conference abstracts, editorials, letters, patents, non-peer-reviewed articles, and studies not published in English were also omitted. Furthermore, research using nanomaterials that had no obvious connection to the delivery of phytochemical drugs or their therapeutic use was excluded. In compliance with PRISMA guidelines, this selective strategy made sure that the final qualitative synthesis contained only methodologically sound and translationally relevant studies (Moher et al., 2009; Page et al., 2021).

2.3 Study Selection and Data Extraction

To guarantee transparency and repeatability, the research selection procedure was carried out step-by-step in compliance with PRISMA principles (Moher et al., 2009; Page et al., 2021). All of the records that were found after the thorough database search were imported into a reference management program, and duplicate articles were eliminated. The relevance of titles and abstracts to phytomedicine research and medication development facilitated by nanotechnology was independently screened. At this point, articles that blatantly failed to satisfy the predetermined inclusion criteria were eliminated. The remaining publications were then subjected to full-text screening in order to determine eligibility based on study design, kind of nanocarrier, and phytochemical significance.

Data extraction was carried out utilizing a pre-made, standardized extraction form to ensure consistency between investigations. The retrieved data included the following: author and publication year; kind of phytochemical or plant extract; nanocarrier system and formulation technique; particle size and physicochemical properties; administration route; therapeutic indication; and significant pharmacological or pharmacokinetic effects. When available, information on toxicity, enhanced bioavailability, and performance in comparison to

conventional formulations was also recorded. Any disputes that emerged during study selection or data extraction were resolved through discussion in order to lessen selection bias and enhance data accuracy. The gathered data were qualitatively analyzed and condensed into tables and figures to facilitate comparison and highlight translational trends in nano-phytomedicine research (Liberati et al., 2009; Siddaway et al., 2019).

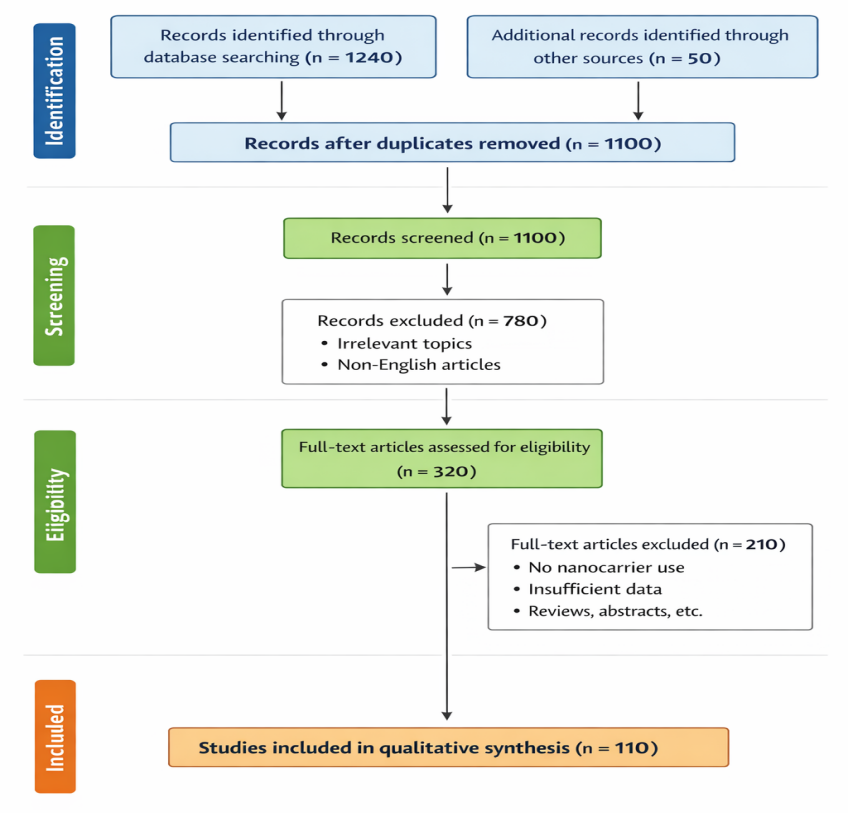

Fig 1: PRISMA Flow Diagram

2.4 Quality and Risk-of-Bias Assessment

To guarantee the dependability and strength of the evidence compiled in this review, the methodological quality and bias risk of the included research were methodically evaluated. Based on the study design, appropriate and validated evaluation instruments were chosen. The SYRCLE risk-of-bias tool, which looks at areas like selection bias, performance bias, detection bias, attrition bias, and reporting bias, was used to assess in vivo animal experiments (Hooijmans et al., 2014). As advised for nanomedicine research, in vitro studies were evaluated critically using predetermined quality criteria, such as adequate experimental controls,

reproducibility of nanocarrier characterization, and transparency in outcome reporting (Fadeel et al., 2018).

The Cochrane Risk of Bias tool was used for clinical trials when appropriate to evaluate blinding, allocation concealment, randomization techniques, and outcome data completeness (Higgins et al., 2011). Based on an overall evaluation across domains, each study was separately classified as having a low, moderate, or high risk of bias. To reduce subjective bias, disagreements in quality rating were settled by consensus. In compliance with PRISMA principles, the quality and risk-of-bias evaluation results were integrated into the qualitative synthesis and interpretation of findings, enabling a stronger emphasis on high-quality and translationally relevant evidence (Moher et al., 2009; Page et al., 2021).

3. Why Nanotechnology for Phytomedicine?

3.1 Key Barriers in Phytochemical Drug Development

Despite phytochemicals' enormous therapeutic potential, there are still a number of intrinsic physicochemical and biological obstacles that prevent them from being successfully translated into clinically useful medicinal molecules. Many bioactive substances produced from plants, such as terpenoids, polyphenols, and flavonoids, have limited membrane permeability and poor water solubility, which lead to poor absorption and unpredictable bioavailability after oral treatment (Yadav et al., 2014; Ganesan et al., 2018). Furthermore, phytochemicals are frequently chemically unstable and can be broken down by light, heat, oxygen, and the pH of the gastrointestinal tract, which reduces their medicinal efficacy and shelf life (Anand et al., 2007).

Rapid metabolism and systemic clearance, especially via first-pass hepatic metabolism, which severely restricts plasma exposure and therapeutic concentrations at the target site, is another key obstacle (Patel et al., 2018). Additionally, nonspecific tissue distribution and poor target specificity may require greater dosages, raising the possibility of toxicity and off-target effects (Bonifácio et al., 2014). Standardization, quality control, and regulatory approval are further complicated by the intricate chemical makeup and batch-to-batch variability of plant extracts (Ekor, 2014). All of these drawbacks highlight the necessity of sophisticated delivery methods, like systems based on nanotechnology, to improve the pharmacological efficacy and translational viability of phytochemical therapeutic candidates.

3.2 How Nanotechnology Overcomes These Barriers

By modifying the physicochemical and biological characteristics of phytochemical drugs, nanotechnology-based drug delivery systems offer strategic answers to the basic constraints related to phytochemical drug development. By decreasing particle size and increasing surface area, nanoencapsulation dramatically increases the perceived solubility and dissolution rate of poorly water-soluble phytochemicals, boosting systemic bioavailability and gastrointestinal absorption (Anand et al., 2007; Date et al., 2010). Labile phytochemicals are further shielded against chemical deterioration and enzymatic metabolism by lipid- and polymer-based nanocarriers, maintaining their biological activity both during storage and following delivery (Mehnert & Mäder, 2012).

Additionally, controlled and sustained drug release made possible by nanocarrier systems reduces the frequency of dosage and minimizes systemic toxicity by extending circulation time and maintaining therapeutic drug concentrations over extended periods of time (Danhier et al., 2012). PEGylation and ligand-mediated targeting are two surface modification techniques that increase biodistribution and site-specific delivery, increasing accumulation at disease sites while reducing exposure off-target (Patra et al., 2018). Significantly, nanotechnology improves phytochemical intracellular delivery and cellular uptake via endocytic pathways, which is especially helpful in cancer and neurodegenerative diseases where drug access is restricted by biological barriers like the blood–brain barrier (Kumar et al., 2017).

Furthermore, by providing exact control over particle size, drug loading, and release kinetics, nanotechnology helps standardize and reproduce phytomedicine formulations, resolving batch-to-batch variability problems that are present in plant-based products (Bonifácio et al., 2014). When taken as a whole, these benefits present nanotechnology as a revolutionary platform for enhancing the safety, therapeutic efficacy, and translational potential of phytochemical-based medication candidates.

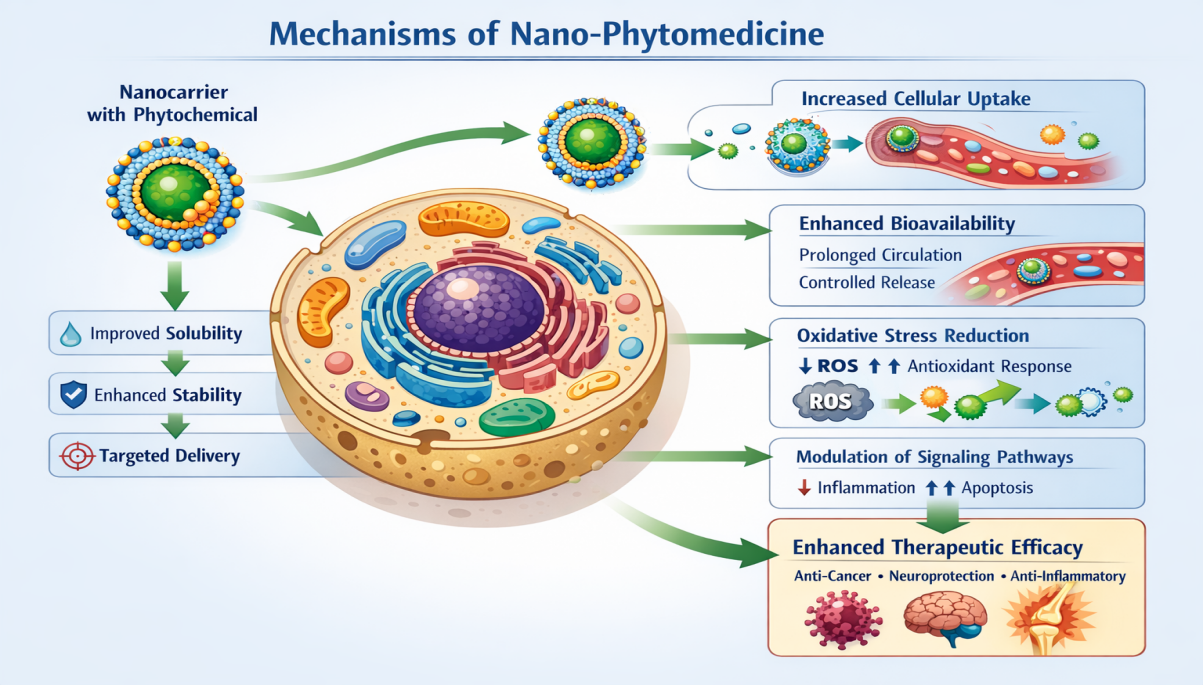

Figure 2: Mechanistic schematic—how nanocarriers enhance phytomedicine efficacy

4. High-Value Nanocarrier Systems for Phytomedicines

4.1 Polymeric Nanoparticles

Because of their biodegradability, biocompatibility, and formulation diversity, polymeric nanoparticles are among the most researched and valuable nanocarrier systems for phytomedicine delivery. Plant-derived bioactive compounds are frequently encapsulated in natural and synthetic polymers, such as poly(lactic-co-glycolic acid) (PLGA), chitosan, alginate, and polyethylene glycol (PEG), to improve solubility, prevent degradation, and provide controlled drug release (Kumari et al., 2010). In order to maximize the pharmacokinetics and therapeutic efficacy of phytochemicals, these devices enable precise control of particle size, surface charge, and drug loading.

By lowering first-pass metabolism and encouraging sustained release, polymeric nanoparticles have shown great promise in increasing the oral bioavailability and systemic circulation time of poorly soluble phytochemicals like curcumin, quercetin, and epigallocatechin gallate (EGCG) (Gao et al., 2012). Furthermore, enhanced cellular uptake and tissue-specific distribution are made possible by surface functionalization with targeted ligands or hydrophilic polymers, especially in cancer and inflammatory illnesses (Mohanraj & Chen, 2006).

Significantly, polymeric nanocarriers facilitate reproducibility and scalability, resolving important translational issues in the creation of phytomedicine drugs. Their importance as a platform technology for bringing nano-enabled phytopharmaceuticals toward clinical application is further highlighted by their established safety profiles and regulatory acceptability (Parveen et al., 2012).

4.2 Lipid-Based Nanocarriers

4.2.1 Liposomes

Because of their biocompatible phospholipid bilayer structure, which allows them to encapsulate both hydrophilic and lipophilic phytochemicals, liposomes are among the most clinically proven lipid-based nanocarriers for phytomedicine delivery. Liposomes improve medication solubility, shield phytochemicals from chemical and enzymatic degradation, and increase cellular absorption by imitating biological membranes (Allen & Cullis, 2013). Particularly in cancer and inflammatory illnesses, liposomal encapsulation of plant-derived substances like curcumin, berberine, and silymarin has shown improved pharmacokinetic profiles, decreased systemic toxicity, and improved therapeutic efficiency (Sercombe et al., 2015). Moreover, extended circulation and site-specific distribution are made possible by surface modification of liposomes with polyethylene glycol or targeting ligands, which promotes translational and clinical usefulness (Bulbake et al., 2017).

4.2.2 Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

Advanced lipid-based systems, such as solid lipid nanoparticles and nanostructured lipid carriers, are intended to get beyond the stability and drug-loading constraints of conventional lipid formulations. Solid lipids stabilized by surfactants make up SLNs, which provide enhanced physical stability, controlled release, and protection of delicate phytochemicals (Mukherjee et al., 2009). NLCs, which use a mixture of solid and liquid lipids to create an imperfect lipid matrix that improves encapsulation efficiency and reduces drug ejection during storage, were developed in response to SLNs' limited drug-loading capacity (Müller et al., 2011). Phytochemicals like resveratrol, curcumin, and quercetin have demonstrated improved therapeutic effects, increased skin and oral absorption, and superior bioavailability when delivered via SLN and NLC (Naseri et al., 2015). Their scalability, physical stability, and

favorable safety profiles make SLNs and NLCs highly valuable nanocarrier platforms for phytomedicine-based drug development.

4.3 Nanoemulsions and SNEDDS

With droplet diameters usually between 20 and 200 nm, nanoemulsions are isotropic, thermodynamically stable dispersions of water and oil stabilized by surfactants. They provide a number of benefits for the administration of phytochemicals, such as increased solubility, better gastrointestinal absorption, and defense against chemical and enzymatic degradation of labile bioactives (Shakeel et al., 2007). For lipophilic plant-derived substances like curcumin, quercetin, and resveratrol, nanoemulsions have been effectively used; preclinical research has shown better therapeutic efficacy and greater oral bioavailability (Singh et al., 2017). Rapid drug release and absorption are made possible by the large interfacial area provided by the small droplet size.

When self-nanoemulsifying drug delivery systems (SNEDDS) come into contact with gastrointestinal fluids, isotropic mixes of oils, surfactants, and co-surfactants spontaneously produce fine oil-in-water nanoemulsions. Without using high-energy emulsification methods, SNEDDS improve oral bioavailability by addressing the primary obstacle of phytochemicals' weak solubility (Pouton, 2006). When compared to traditional formulations, SNEDDS formulations of curcumin, silymarin, and berberine have demonstrated improved solubility, greater plasma concentrations, and superior pharmacokinetics (Date et al., 2010). SNEDDS are a useful and valuable nanocarrier for converting phytochemicals into potent treatments because of their scalability, simplicity of production, and patient-friendly oral delivery.

Overall, nanoemulsions and SNEDDS provide flexible and efficient platforms for overcoming solubility, stability, and bioavailability challenges, complementing polymeric and lipid-based nanoparticles in nano-phytomedicine development.

4.4 Green-Synthesized Nanoparticles

Green-synthesized nanoparticles are an environmentally friendly and sustainable method for creating nano-phytomedicines. Green synthesis eliminates the need for hazardous chemicals and high-energy procedures by using plant extracts, microbial metabolites, or biomolecules as reducing and stabilizing agents, in contrast to traditional chemical and physical nanoparticle

synthesis methods (Iravani, 2014). In addition to being environmentally sustainable, this method gives the phytochemicals utilized in synthesis intrinsic medicinal qualities, which may increase the biological activity of the final nanoparticles (Singh et al., 2018).

These green nanoparticles have demonstrated improved bioavailability, antioxidant, antibacterial, and anticancer properties when used to deliver bioactive chemicals including curcumin, quercetin, and silver nanoparticles capped with plant extracts (Ahmed et al., 2016). Green synthesis also makes it possible to produce nano-phytomedicines in a scalable and economical manner, which lowers the obstacles to their commercial and translational usage. All things considered, green-synthesized nanoparticles combine environmentally friendly nanotechnology with the therapeutic potential of phytochemicals, making them a valuable approach for the creation of next-generation phytopharmaceuticals.

Table 1: Types of Nanocarriers for Phytochemical

Nanocarrier Type	Composition	Advantages	Limitations
Liposomes	Phospholipids	Biocompatible, versatile	Stability issues
Solid Lipid Nanoparticles (SLNs)	Solid lipid core	Controlled release	Drug expulsion during storage
Nanostructured Lipid Carriers (NLCs)	Lipid mix (solid + liquid)	High drug loading	Complexity in formulation
Polymeric Nanoparticles	Biodegradable polymers	Sustained release	Potential cytotoxicity
Nanoemulsions	Oil-in-water	Improved solubility	Stability
Micelles	Amphiphilic molecules	Solubilization of hydrophobic drugs	Low stability upon dilution

5. Disease-Driven Applications of Nano-Phytomedicines

5.1 Cancer Therapy

The anticancer potential of plant-derived bioactives and the requirement for targeted distribution to lower systemic toxicity make cancer a prominent focus of nano-phytomedicine. When compared to traditional formulations, the administration of phytochemicals including

curcumin, resveratrol, and paclitaxel via nanotechnology enhances their solubility, stability, and bioavailability (Anand et al., 2010; Li et al., 2016). In a variety of cancer models, curcumin-loaded nanoparticles, liposomes, and nanoemulsions improve cellular uptake, trigger apoptosis, and stop tumor development (Yallapu et al., 2012). Resveratrol nanoformulations inhibit angiogenesis and metastasis while enhancing circulation and tumor targeting (Shankar et al., 2013). Paclitaxel has improved solubility, decreased multidrug resistance, and a greater therapeutic index in lipid-based nanoparticles or polymeric micelles (Zhang et al., 2014). These tactics maximize effectiveness while reducing systemic toxicity by utilizing passive EPR-based targeting and, in certain situations, active ligand-mediated delivery.

Table 2: Nanoformulations of key phytochemicals

Natural Compound	Nanoformulation	Target Disease/Application	Key Outcomes
Curcumin	PLGA nanoparticles	Alzheimer's disease	Improved BBB penetration, neuroprotection
Curcumin	Liposomes	Cancer	Enhanced cytotoxicity, better solubility
Resveratrol	Solid lipid nanoparticles	Alzheimer's, Diabetes	Improved bioavailability
Quercetin	PLGA nanoparticles	Diabetes, oxidative stress	Increased antioxidant effect
Curcumin	Self-nanoemulsifying systems	Anti-inflammatory	Enhanced solubility & absorption

5.2 Inflammatory and Metabolic Disorders

By increasing the bioavailability and effectiveness of plant-derived bioactives, nano-phytomedicine techniques offer promise in the treatment of inflammatory and metabolic disorders, such as diabetes, arthritis, and cardiovascular diseases. Although they have anti-inflammatory, antioxidant, and metabolic regulating properties, phytochemicals including curcumin, quercetin, resveratrol, and berberine are restricted by their poor solubility and quick metabolism (Gupta et al., 2013; Zhang et al., 2016). Targeted distribution, prolonged circulation, and improved absorption are all made possible by encapsulation into nanocarriers, such as polymeric nanoparticles, lipid-based nanoparticles, and nanoemulsions. While resveratrol and quercetin nanoformulations enhance glycemic control and lipid profiles in

diabetes and cardiovascular models (Xie et al., 2017; Zeng et al., 2018), curcumin-loaded nanoparticles lower pro-inflammatory cytokines and oxidative stress in arthritis and inflammatory bowel disease models (Gopinath et al., 2018). Nanoformulations also allow sustained release, reducing dosing frequency and toxicity, highlighting their potential as multi-targeted therapies for inflammatory and metabolic disorders.

5.3 Neurodegenerative Disorders

The limited blood–brain barrier (BBB) and poor solubility or quick metabolism of substances like curcumin, resveratrol, quercetin, and ginsenosides make phytochemical therapies difficult to use for neurodegenerative diseases including Alzheimer's, Parkinson's, and Huntington's diseases. Through transcytosis or receptor-mediated transport, nanocarriers like lipid-based nanoparticles, polymeric nanoparticles, and nanoemulsions increase CNS bioavailability; on the other hand, surface modifications like PEGylation and transferrin conjugation improve targeting and decrease systemic clearance. Curcumin and resveratrol-loaded nanoparticles have been shown in preclinical studies to enhance cognitive function, decrease amyloid plaques, and reduce neuroinflammation. These findings demonstrate that nano-phytomedicine strategies enable targeted BBB penetration, sustained release, and site-specific therapeutic action, offering promising approaches for managing neurodegenerative disorders.

5.4 Antimicrobial and Antiviral Applications

The antibacterial and antiviral properties of plant-derived bioactives are improved by nano-phytomedicine techniques. The broad-spectrum activity of phytochemicals including curcumin, quercetin, eugenol, and EGCG is constrained by their poor solubility, low stability, and quick degradation (Hemaiswarya et al., 2008; Li et al., 2016). Polymeric nanoparticles, liposomes, solid lipid nanoparticles, and nanoemulsions are examples of nanocarriers that enhance solubility, shield substances from deterioration, and allow for tailored administration. Gram-positive and Gram-negative bacteria, including those resistant to multiple drugs, are more effectively inhibited by curcumin-loaded nanoparticles and chitosan-coated lipid nanoparticles (Rai et al., 2016; Singh et al., 2017). By boosting bioavailability and intracellular penetration, resveratrol or EGCG nanoformulations enhance antiviral action against influenza, HIV, and herpes viruses (Vivek et al., 2017; Xu et al., 2019). Nano-phytomedicines are attractive prospects for next-generation anti-infective treatments because of their large surface

area and small nanoparticle size, which also enable the co-delivery of many phytochemicals for synergistic effects.

6. Pharmacokinetics, Safety, and Translational Value

6.1 Bioavailability and Targeted Delivery Outcomes

The pharmacokinetic constraints of traditional phytochemicals are overcome by nano-phytomedicines, which improve bioavailability and allow tailored delivery. Polymeric nanoparticles, liposomes, solid lipid nanoparticles, and nanoemulsions are examples of nanocarriers that enhance solubility, prevent degradation of labile compounds, and permit controlled release, leading to extended circulation and increased plasma concentrations (Sanna et al., 2014; Paliwal et al., 2016). Both passive techniques, such as the EPR effect, and active tactics employing ligand-functionalized carriers for particular cellular recognition are used to achieve targeting (Patra et al., 2018; Saraiva et al., 2016). Preclinical research highlights the translational potential of nanoformulations of curcumin, resveratrol, quercetin, and paclitaxel by demonstrating increased bioavailability, improved tissue accumulation, and superior pharmacodynamic outcomes when compared to free drugs (Tiwari et al., 2014; Mohanty et al., 2018).

6.2 Toxicity and Nanotoxicological Concerns

Although phytochemicals' medicinal potential is increased by nanocarriers, they also present special nanotoxicological difficulties. The size, shape, surface charge, and composition of nanoparticles might influence how they interact with biological systems, possibly leading to oxidative stress, inflammation, cytotoxicity, or organ accumulation (Elsaesser & Howard, 2012; Fadeel et al., 2018). Although biodegradable lipids and polymers (such PLGA and chitosan) typically lessen systemic toxicity, concerns may still arise from dosage, repetitive administration, and surface changes (Bhattacharya et al., 2016). In vitro cytotoxicity, hemocompatibility, genotoxicity, and immunotoxicity testing, as well as in vivo biodistribution and acute/chronic toxicity investigations, are necessary for safety evaluation. Additionally, accurate characterisation, stability, and repeatability of nanocarriers are required for regulatory compliance (Kumar et al., 2019). The necessity for standardized nanotoxicological techniques in translational nano-phytomedicine research is highlighted by the fact that well-designed, biodegradable plant-based nanocarriers can generally attain positive safety profiles.

6.3 Translational Challenges

Despite encouraging preclinical results, there are a number of translational obstacles with nano-phytomedicines. Because it is challenging to maintain crucial quality parameters such particle size, drug loading, and release kinetics at large scale, scalability, batch-to-batch reproducibility, and stability continue to be significant obstacles, especially for complex or hybrid nanocarriers (Patra et al., 2018; Agrawal et al., 2018). Dose optimization is complicated by pharmacokinetic variability, which is impacted by interactions with plasma proteins and the mononuclear phagocyte system (Danhier et al., 2012). Extensive preclinical and clinical evaluation is required for nanomedicines, particularly plant-based formulations, due to safety concerns, long-term toxicity, and changing regulatory frameworks (Fadeel et al., 2018). Intellectual property concerns, cost-effectiveness, and market acceptance are further obstacles that call for distinct clinical benefits above traditional treatments. The combination of nanotechnology with phytochemicals offers significant potential for safe and effective medicines, but overcoming these obstacles requires interdisciplinary cooperation, reliable manufacturing techniques, and standardized evaluation protocols.

7. Clinical Progress and Regulatory Perspective

7.1 Status of Clinical Trials in Nano-Phytomedicine

Although it is progressing, the clinical application of nano-phytomedicines is still restricted in comparison to traditional medications. The majority of studies use nanocarriers including liposomes, polymeric nanoparticles, and solid lipid nanoparticles to increase the bioavailability and effectiveness of phytochemicals like curcumin, resveratrol, and quercetin (Liu et al., 2016; Kotha & Luthria, 2019). In comparison to free curcumin, curcumin-loaded nanoparticles and liposomal curcumin have demonstrated increased plasma levels, better tolerability, and initial efficacy in Phase I/II trials for cancer, inflammatory, and neurological illnesses (Dhillon et al., 2008; Kanai et al., 2012). Resveratrol nanoformulations with enhanced absorption and safety are being tested for metabolic syndrome and cardiovascular disorders (Patel et al., 2018).

However, there are still few late-phase trials, and clinical translation is slowed by regulatory issues like standardized characterisation, safety regulations, and quality control. Comprehensive pharmacokinetic, toxicological, and manufacturing data are required by authorities like the FDA and EMA; these requirements are stricter for complicated nano-

phytomedicines (McClements, 2018). Large-scale, well planned studies are necessary to determine clinical efficacy, long-term safety, and regulatory compliance, even though early-phase trials offer promising findings on safety and bioavailability.

7.2 Regulatory Challenges in Approval

Because of the distinct physicochemical characteristics, multifunctionality, and hybrid composition of nanocarrier systems, which set them apart from traditional small-molecule or herbal medications, the regulatory environment for nano-phytomedicines is still complicated. Before approving a product, regulatory bodies like the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and the Central Drugs Standard Control Organization (CDSCO, India) want thorough quality, safety, and efficacy data (Ruggiero et al., 2020; McClements, 2018).

Key regulatory challenges include:

1. **Characterization and Standardization:** Particle size, polydispersity, surface charge, encapsulation effectiveness, release kinetics, and stability must all be thoroughly examined for nano-phytomedicines. Regulatory evaluation is challenging since there are no widely recognized, established procedures.

2. **Safety and Toxicology:** Unexpected biological interactions, such as immunogenicity, cytotoxicity, or long-term organ accumulation, may occur with nanocarriers. Extensive preclinical nanotoxicological examination, including acute, chronic, and genotoxicity research, is required by regulatory bodies (Fadeel et al., 2018).

3. **Manufacturing and Reproducibility:** Batch-to-batch consistency, sterility, and stability must be guaranteed when scaling up nanophytomedicine formulations, which is frequently difficult for hybrid systems or green-synthesized nanoparticles (Patra et al., 2018).

4. **Regulatory Classification:** Ambiguity in regulatory pathways may result from nano-phytomedicines falling between dietary supplements, herbal medicines, and nanopharmaceuticals. Although precise criteria for plant-based nanocarriers are still being developed, organizations such as the FDA and EMA have released guidance sheets on nanomedicines (Ruggiero et al., 2020).

5. **Clinical Evidence:** Regulators stress the necessity of well planned clinical trials that show bioequivalence, pharmacokinetics, efficacy, and safety—all of which are still scarce for nano-phytomedicines (Liu et al., 2016).

To expedite the transition of nano-phytomedicines from bench to bedside, it is necessary to solve these regulatory difficulties by strict standardization, thorough safety evaluation, repeatable manufacturing, and early contact with regulatory authorities.

8. Future Directions and Emerging Opportunities

At the nexus of sophisticated nanotechnology, artificial intelligence (AI), and personalized medicine, nano-phytomedicine research holds great promise for improving patient outcomes and therapeutic efficacy. The rational development of optimal nanocarriers for complex phytochemicals is accelerated by AI-guided nanoformulation design, which enables predictive modeling of nanoparticle characteristics, drug release kinetics, and tissue-specific delivery (Zhang et al., 2021). These technologies enable the tailoring of nano-phytomedicine regimens based on patient-specific characteristics, such as genetic profile, metabolic condition, and disease phenotype, when combined with personalized phytomedicine techniques. This maximizes efficacy while minimizing side effects (Li et al., 2022).

Furthermore, incorporating traditional medical systems like Ayurveda, TCM, and ethnopharmacology offers a wealth of bioactive phytochemicals and therapeutic knowledge that can be updated with nanotechnology for improved bioavailability, targeted delivery, and controlled release (Patwardhan et al., 2005). By connecting traditional knowledge with cutting-edge research to address complicated disorders, such multidisciplinary approaches hold the potential to transform nano-phytomedicine from experimental formulations into clinically relevant, sustainable, and patient-centered therapies.

9. Limitations of Current Evidence

Strong clinical translation is hampered by a number of significant shortcomings in the present evidence base for nano-phytomedicines, despite significant advancements in preclinical research. First, cross-study comparisons and meta-analyses are difficult due to the absence of standardized experimental models for assessing the pharmacokinetics, biodistribution, efficacy, and toxicity of nano-phytomedicines (Fadeel et al., 2018; Patra et al., 2018).

Reproducibility and result interpretation are further complicated by variations in nanoparticle manufacturing, characterisation, and dosage protocols.

Second, well-designed clinical trials are hard to come by. Only a small number of nano-phytomedicines have advanced to human trials, and the majority are early-phase studies concentrating on safety or pharmacokinetics rather than efficacy, despite the fact that numerous preclinical studies show improved bioavailability, targeted delivery, and therapeutic outcomes (Liu et al., 2016). This disparity highlights the necessity of thorough clinical testing, long-term safety evaluation, and standardized outcomes to confirm these formulations' translational potential.

All of these drawbacks show that in order to fully achieve the therapeutic potential of nano-phytomedicines, standardized procedures, reliable preclinical-to-clinical pipelines, and regulatory alignment are required.

10. Conclusion

By combining the therapeutic potential of bioactives produced from plants with cutting-edge nanotechnology, nano-phytomedicine enables improved solubility, bioavailability, targeted delivery, and controlled release. Early clinical trials show better pharmacokinetics and safety profiles, while preclinical research shows its effectiveness in models of cancer, neurological diseases, metabolic disorders, and infectious diseases. Regulatory obstacles, standardization problems, and a lack of clinical data continue to be major obstacles despite encouraging results. Clinical translation can be accelerated by future options like as AI-guided formulation design, individualized phytomedicine, and interaction with standard medicine systems. All things considered, nano-phytomedicine has the potential to bridge ancient knowledge with contemporary drug delivery advances, converting traditional phytotherapy into safe, efficient, and patient-centered therapies.

11. Acknowledgement

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12. Conflict of Interest

The author declares no conflict of interest related to the content of this review.

13. References

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