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Nano-enhanced phytomedicine: A review of nanocarrier systems for targeted delivery of plant-derived bioactives in chronic disease therapy

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ABSTRACT

Background/objectives: Chronic diseases such as cancer, diabetes, neurodegenerative disorders, and cardiovascular diseases continue to pose significant global health challenges. Phytomedicine offers therapeutic potential through antioxidant, anti-inflammatory, and disease-modifying properties, yet clinical effectiveness is constrained by poor solubility, low bioavailability, and lack of targeted delivery. This review assesses how nanocarrier systems have been employed to overcome these pharmacokinetic limitations and enhance the therapeutic efficacy of phytochemicals in chronic disease management.

Methods: A systematic narrative review was conducted by searching PubMed, Scopus, Web of Science, and Google Scholar using the following keyword set: ("nanocarrier*" OR "nanoparticle*" OR "nanotechnology" OR "nanoformulation*") AND ("phytochemical*" OR "phytomedicine" OR "plant-based" OR "plant-derived" OR "herbal") AND ("chronic disease*" OR "cancer" OR "diabetes" OR "cardiovascular" OR "neurodegeneration" OR "Alzheimer" OR "targeted drug delivery" OR "bioavailability"). The search covered peer-reviewed publications from 2013 to 2025. Searches were conducted in title, abstract, and keyword fields. English-language research articles, reviews, and book chapters were included. The search yielded over 4200 publications; after deduplication and relevance screening, 160 studies were retained for detailed analysis.

Results: Nanocarriers including lipid-based nanoparticles, polymeric nanoparticles, dendrimers, metallic nanoparticles, nanoemulsions, mesoporous silica nanoparticles, and emerging plant-derived exosomes significantly improved the solubility, stability, and targeted delivery of key phytochemicals such as curcumin, quercetin, EGCG, berberine, and resveratrol. Enhanced bioavailability and tissue-specific delivery reduced systemic toxicity and improved preclinical and early-stage clinical efficacy. Challenges remain regarding production scalability, regulatory harmonization, and nanotoxicity profiling.

Conclusion: Nanoformulated phytochemicals represent a promising frontier in chronic disease therapy. Future research should prioritize overcoming translational barriers, advancing green and biogenic nanotechnology, and developing AI-assisted personalized nano-phytomedicine platforms.

1. Introduction

The revived interest in plant-derived chemicals as therapeutic agents reflects growing awareness of the medicinal benefits of natural products alongside the escalating burden of chronic non-communicable diseases. Contemporary interest in phytomedicine rests on a substantial

Abbreviations: AuNPs, Gold Nanoparticles; AgNPs, Silver Nanoparticles; BBB, Blood-Brain Barrier; CVD, Cardiovascular Disease; EGCG, Epigallocatechin-3-gallate; EMA, European Medicines Agency; EPR, Enhanced Permeability and Retention; EVs, Extracellular Vesicles; FDA, Food and Drug Administration; GMP, Good Manufacturing Practice; MSNs, Mesoporous Silica Nanoparticles; NDs, Neurodegenerative Disorders; NLCs, Nanostructured Lipid Carriers; PCL, Polycaprolactone; PEG, Polyethylene Glycol; PEGylation, Surface Modification with Polyethylene Glycol; PLGA, Poly(lactic-co-glycolic acid); PNPs, Polymeric Nanoparticles; ROS, Reactive Oxygen Species; SEDDS, Self-Emulsifying Drug Delivery Systems; SLNs, Solid Lipid Nanoparticles.

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pharmacological and biochemical body of knowledge that has validated the therapeutic potential of plant secondary metabolites (Mukherjee et al., 2017). Key phytochemicals curcumin from turmeric, resveratrol from grapes, quercetin from onions, and berberine from Berberis species demonstrate broad pharmacological activities including antioxidant, anti-inflammatory, antibacterial, anticancer, and neuroprotective actions. These compounds target multiple molecular pathways, making them particularly useful for complex chronic diseases such as cancer, diabetes, cardiovascular disease, and neurodegenerative disorders (Upadhyay and Dixit, 2015).

Despite this promise, significant pharmacokinetic and pharmacodynamic limitations impede the practical implementation of phytomedicine. Most bioactive plant compounds have low aqueous solubility, restricting gastrointestinal absorption and systemic bioavailability (Dima et al., 2020). The majority also undergo rapid metabolic breakdown and excretion, yielding short plasma half-lives and insufficient concentrations at target sites (Parthasarathy et al., 2025). The absence of site-specific delivery necessitates higher doses, raising off-target toxicity risks and reducing patient compliance challenges especially critical in chronic disorders requiring sustained, long-term drug exposure (Haines et al., 2024; Mbata et al., 2024). As a result, despite impressive preclinical findings, many phytochemicals fail to produce comparable outcomes in clinical trials.

Nanotechnology has emerged as a transformative tool to address these barriers as shown in Fig. 1. Plant-derived compounds can be encapsulated in nanocarrier systems (liposomes, nanoemulsions, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, metallic nanoparticles, and increasingly, plant-derived exosomes) to improve physicochemical stability, bioavailability, and target specificity (Kothapalli and Vasanthan, 2024). These systems enhance solubility, protect phytoconstituents from enzymatic and chemical degradation, allow regulated and prolonged release, and actively or passively target specific tissues or cells (Dutt et al., 2023). Stimuli-responsive and multifunctional delivery systems that respond to pH, temperature, or enzyme activity further improve therapeutic performance and reduce side effects (Fatima et al., 2024).

This review comprehensively discusses the role of nanotechnology in improving the therapeutic value of phytomedicine for chronic disease treatment. It covers major phytochemicals and their limitations, the diversity of nanocarrier systems and their structural and functional attributes, disease-specific applications (cancer, neurodegeneration, cardiovascular disease, and metabolic disorders), clinical translation status, emerging strategies including biogenic and green nanocarriers, and future research directions. Where relevant, mechanistic data and comparative analyses are provided to supplement the narrative synthesis.

2. Methodology

2.1. Search strategy

This narrative review followed a systematic search approach. Four electronic databases were searched: PubMed, Scopus, Web of Science, and Google Scholar. The full search syntax used was:

("nanocarrier*" OR "nanoparticle*" OR "nanotechnology" OR "nanoformulation*" OR "nanomedicine" OR "nano-drug delivery") AND ("phytochemical*" OR "phytomedicine" OR "phytoconstituent*" OR "plant-based" OR "plant-derived" OR "herbal" OR "bioactive compound*" OR "polyphenol*") AND ("chronic disease*" OR "cancer" OR "tumour" OR "diabetes" OR "cardiovascular" OR "neurodegeneration" OR "Alzheimer*" OR "Parkinson*" OR "inflammation" OR "liver disease" OR "metabolic syndrome" OR "targeted drug delivery" OR "bioavailability" OR "drug delivery system*")

Searches were applied to title, abstract, and keyword fields. The review was restricted to English-language peer-reviewed journal articles, systematic reviews, book chapters, and clinical trial reports published between January 2013 and April 2025.

2.2. Inclusion and exclusion criteria

Studies were included if they: (1) investigated nanocarrier-based delivery of plant-derived phytochemicals; (2) reported pharmacokinetic or therapeutic outcomes in vitro, in vivo, or clinical settings; and (3) addressed at least one of the six chronic disease areas reviewed (cancer, neurodegeneration, cardiovascular disease, diabetes/metabolic syndrome, liver disease, or inflammatory/autoimmune disorders). Studies were excluded if they: (1) focused exclusively on synthetic drug delivery without phytochemical relevance; (2) were conference

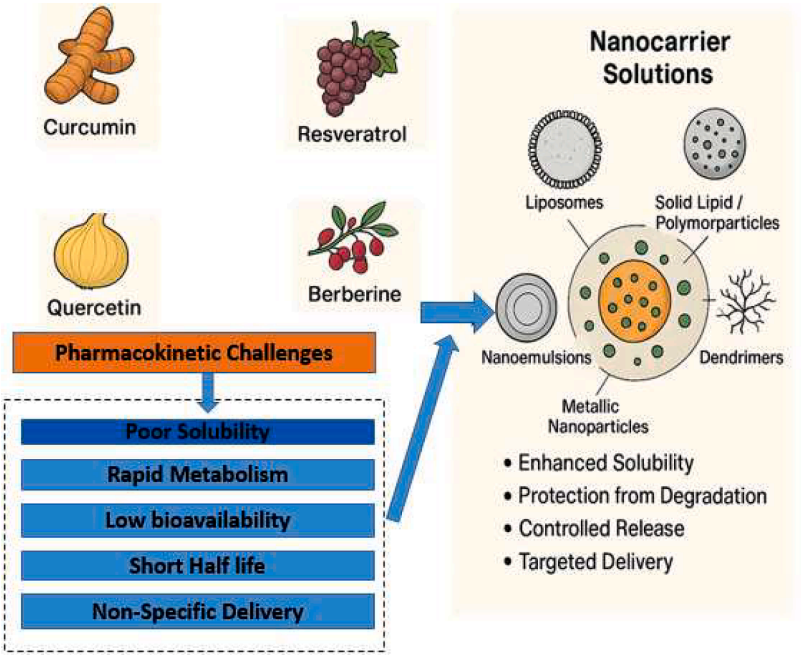


Fig. 1. Biochemical properties and nanotechnological advances in phytomedicine.

abstracts without full-text publication; or (3) were published in languages other than English.

2.3. Study selection and data extraction

The initial broad search returned over 4200 publications. After automated deduplication, title and abstract screening removed 3800 records that did not meet inclusion criteria. Full-text review of the remaining 400 records led to the inclusion of 160 publications for detailed analysis and synthesis. Data extracted from each study included: phytochemical identity, nanocarrier type, disease target, pharmacokinetic outcomes, mechanistic findings, clinical trial stage (where applicable), and key limitations.

2.4. Determination of key research fronts

Research fronts were identified using frequency analysis of phytochemical and nanocarrier types cited across included studies, supplemented by citation mapping. Phytochemicals appearing in >10% of included studies were classified as 'major' and are discussed in dedicated subsections. Nanocarrier types were categorized by their structural class (lipid-based, polymer-based, inorganic, hybrid, and biogenic), and disease domains were selected based on their frequency of coverage in the nanophytomedicine literature.

2.5. Methodological limitations

Several methodological limitations are acknowledged. First, this review is a narrative rather than quantitative meta-analysis; therefore, pooled statistical estimates of effect sizes are not provided. Second, the search syntax, while comprehensive, may not have captured all relevant literature, particularly from specialized journals or grey literature. Third, the majority of included primary studies are preclinical (in vitro or small animal models), limiting the strength of translational conclusions. Fourth, inter-study variability in nanoformulation parameters (particle size, drug loading, and encapsulation efficiency) precluded direct quantitative comparisons across studies. Fifth, publication bias toward positive findings may inflate apparent efficacy of nanoformulations. These limitations should be considered when interpreting the conclusions of this review.

3. Novelty and differentiation from existing reviews

A large body of literature comprising over 115 published reviews addresses various aspects of nanophytomedicine delivery. Reviewer-identified similar reviews include those by Chauhan et al. (2024); Elmowafy et al. (2023); Gao et al. (2022); Kothapalli and Vasanthan (2024); Razavi et al. (2024), and Teli et al. (2024). The present review is differentiated from these and other existing reviews in the following key respects:

1) Comprehensive multi-disease scope: Unlike most existing reviews that focus on a single disease (predominantly cancer), this review provides a comparative synthesis across six chronic disease domains cancer, neurodegeneration, cardiovascular disease, diabetes/metabolic syndrome, liver disease, and inflammatory/autoimmune disorders – enabling cross-disease mechanistic comparison.
2) Inclusion of emerging nanocarrier classes: The present review explicitly covers plant-derived exosomes/extracellular vesicles (EVs) and biogenic nanocarriers as emerging platforms not systematically addressed in most prior reviews. This addresses the gap identified by Reviewer #1 regarding novel carrier materials.
3) Full methodology disclosure: Unlike many existing reviews, this paper provides a complete search syntax, inclusion/exclusion criteria, study selection flowchart rationale, and methodological limitations enabling reproducibility and critical appraisal.
4) Comprehensive comparative tables: Novel comparative tables (Tables 4–7) linking nanocarrier benefits, disease-specific mechanisms, phytochemical pharmacokinetics, and translational status were developed and are not present in the majority of existing reviews.
5) Integration of literature: The review incorporates the most recent advances in green nanotechnology, AI-assisted nanoformulation design, and personalized nano-phytomedicine that are absent from reviews published before 2024.

Table 7 below provides a direct comparison of this review against selected recent reviews to illustrate these points of differentiation.

4. Nanocarrier systems in phytomedicine

Nanocarrier systems have transformed phytomedicine delivery by overcoming challenges of low solubility, poor bioavailability, and non-specific distribution of plant-derived bioactive compounds. Nanocarriers are nano-sized delivery vehicles typically between 1 and 1000 nanometers that encapsulate, stabilize, and deliver phytochemicals to sites of action (Nnamani et al., 2025). These systems improve physicochemical stability, pharmacokinetics, and target-tissue interactions (Ioele et al., 2022). Table 1 summarizes the biochemical properties of major phytochemicals and their nanocarrier solutions, while Table 2 details the available nanocarrier platforms.

4.1. Lipid-Based nanocarriers

Lipid-based nanocarriers are among the most widely implemented delivery platforms for plant-based compounds, offering high biocompatibility, scalability, and the capacity to encapsulate both hydrophilic and lipophilic molecules (Gali et al., 2023). Liposomes spherical phospholipid vesicles effectively deliver flavonoids, polyphenols, and essential oils with enhanced cellular uptake due to their similarity to biological membranes (Dutt et al., 2023). Surface functionalization with ligands (antibodies, peptides) enables active tumor or inflamed-tissue targeting (Priya et al., 2022). Solid Lipid Nanoparticles (SLNs) provide controlled release and protect thermolabile phytochemicals, though their low drug-loading capacity is a limitation (Viegas et al., 2023). Nanostructured Lipid Carriers (NLCs) overcome this by incorporating both solid and liquid lipids to create an imperfect crystalline matrix with higher drug loading and reduced drug expulsion during storage (Javed et al., 2022).

4.2. Polymeric nanoparticles

Polymeric nanoparticles offer versatile and tunable phytochemical delivery. Natural polymers chitosan, alginate, and gelatin are biodegradable and mucoadhesive, improving mucosal uptake of phytochemicals such as catechins and quercetin (Mura et al., 2022). Synthetic polymers including FDA-approved PLGA, PEG, and PCL allow programmable degradation and sustained release while protecting phytochemicals from enzymatic breakdown (Pandey et al., 2025). PEGylation reduces opsonization, extends circulation time, and enhances tumor and tissue targetability (Kawish et al., 2024).

4.3. Nanoemulsions and SEDDS

Nanoemulsions (oil-in-water or water-in-oil dispersions with gross surfactants) solubilize water-insoluble phytochemicals including essential oils and terpenoids with high bioavailability due to their nanoscale droplet size. Self-Emulsifying Drug Delivery Systems (SEDDS) isotropic solutions of oils, surfactants, and co-solvents spontaneously form nanoemulsions upon interaction with gastrointestinal fluids, particularly enhancing oral delivery of lipophilic phytoconstituents (Uttreja et al., 2025). Micelles, formed by amphiphilic surfactant aggregation,

Table 1
Biochemical properties and nanotechnological advances in phytomedicine for chronic disease management.

Phytochemical	Source	Key Biochemical Activities	Therapeutic Targets	Pharmacokinetic Limitations	Nanocarrier Solution	Clinical Application
Curcumin	Turmeric (Curcuma longa)	Antioxidant, anti-inflammatory, anticancer, neuroprotective	NF-κB, COX-2, TNF-α, β-amyloid	Poor aqueous solubility; rapid metabolism; low bioavailability	Liposomes, polymeric NPs, solid lipid NPs	Cancer, Alzheimer's, rheumatoid arthritis
Resveratrol	Grapes, berries, peanuts	Cardioprotective, neuroprotective, antidiabetic	SIRT1, AMPK, Nrf2, eNOS	Rapid hepatic metabolism; short half-life; photosensitivity	Nanomicelles, dendrimers, lipid-based NPs	CVD, neurodegenerative disorders, T2 diabetes
Quercetin	Onions, apples, capers	Antioxidant, antiviral, anti-inflammatory, antidiabetic	MAPK, PI3K/Akt, IL-6, histamine receptors	Poor water solubility; limited GI absorption	Nanocrystals, SLNs, nanoemulsions	Asthma, viral infections, metabolic syndrome
Berberine	Berberis species	Hypoglycemic, antimicrobial, lipid-lowering	AMPK, LDL-R, insulin receptors	Low oral bioavailability due to P-gp efflux and first-pass metabolism	Chitosan NPs, nanoemulsions, SEDDS	Type 2 diabetes, hyperlipidemia, infections
EGCG	Green tea (Camellia sinensis)	Antioxidant, anticancer, cardioprotective, anti-obesity	EGFR, VEGF, MMPs	Unstable at physiological pH; poor permeability and bioavailability	Polymeric nanocapsules, liposomes	Breast cancer, CVD, obesity
Baicalein	Scutellaria baicalensis root	Anti-inflammatory, antitumor, anxiolytic	Caspase-3, IL-1β, Nrf2	Low oral absorption; rapid elimination	PLGA NPs, nanomicelles	Colon cancer, anxiety, inflammation
Andrographolide	Andrographis paniculata	Antiviral, hepatoprotective, antidiabetic	NF-κB, TGF-β, insulin signaling	Poor solubility, rapid clearance	Nanoparticles, nanogels	Hepatitis, type 2 diabetes
Withaferin A	Withania somnifera (Ashwagandha)	Anti-inflammatory, antitumor, immunomodulatory	STAT3, Hsp90, VEGF	Poor bioavailability, non-specific delivery	Polymeric micelles, SLNs	Breast/prostate cancer, autoimmune diseases
Silymarin	Milk thistle (Silybum marianum)	Hepatoprotective, antioxidant, antifibrotic	Nrf2, NF-κB, TGF-β	Low solubility, poor absorption, rapid metabolism	Micelles, SLNs, PEGylated NPs	Liver cirrhosis, hepatitis, detoxification
Thymoquinone	Black seed (Nigella sativa)	Antioxidant, anticancer, anti-inflammatory	NF-κB, p53, Bcl-2	Low solubility, instability, rapid metabolism	Lipid NPs, polymeric carriers	Cancer, inflammation, diabetes

Table 2
Nanocarrier systems for phytochemical delivery in phytomedicine.

Nanocarrier Type	Composition	Key Features	Advantages	Representative Phytochemicals	Therapeutic Applications
Liposomes	Phospholipid bilayers	Spherical vesicles mimicking cell membranes	High biocompatibility, targetable, encapsulates hydrophilic & lipophilic compounds	Flavonoids, polyphenols, essential oils	Cancer, inflammation, CVD
Solid Lipid NPs (SLNs)	Solid lipids at body temperature	Lipid matrix solid at room/body temp	Good physical stability, protects thermolabile drugs, controlled release	Berberine, catechins	Neuroprotection, diabetes, infections
Nanostructured Lipid Carriers (NLCs)	Solid + liquid lipids	Imperfect lipid matrix	Higher drug loading, long-term stability	Curcumin, resveratrol	Cancer, diabetes, metabolic disorders
Polymeric NPs (Natural)	Chitosan, alginate, gelatin	Biodegradable, mucoadhesive	Enhances mucosal absorption, low toxicity	Quercetin, EGCG, baicalin	GI, nasal, pulmonary delivery
Polymeric NPs (Synthetic)	PLGA, PEG, PCL	Customizable degradation & release	Sustained release, enzymatic protection	Silymarin, apigenin, thymoquinone	Cancer, neurodegeneration, liver diseases
PEGylated NPs	PEG-functionalized polymers/lipids	Hydrophilic corona prevents opsonization	Extended circulation, improved targeting	Curcumin, kaempferol	Tumor targeting, chronic inflammation
Nanoemulsions	Oil-water systems + surfactants	Small droplet size (20–200 nm)	High solubilization, fast absorption	Essential oils, terpenoids	Topical delivery, antimicrobial, analgesic
SEDDS	Oils, surfactants, co-solvents	Forms nanoemulsion in GI tract	Enhances oral bioavailability of lipophilic drugs	Boswellic acids, withanolides	Oral anti-inflammatory & anticancer use
Micelles	Amphiphilic surfactants	Hydrophobic core for drug solubilization	Protects labile compounds, increases aqueous solubility	Curcumin, silymarin, luteolin	Hepatic, cardiovascular, antioxidant therapy
Gold NPs (AuNPs)	Metallic gold cores	Surface-modifiable, photothermal response	Imaging + therapy (theranostics), targeted delivery	EGCG, luteolin	Cancer (photothermal), imaging
Silver NPs (AgNPs)	Metallic silver cores	Antimicrobial surface properties	Enhances antimicrobial activity, synergistic action	Plant-based antimicrobials	Resistant infections, wound healing
Mesoporous Silica NPs (MSNs)	Silica framework with pores	High surface area and pore volume	High drug loading, precise controlled release	Various polyphenols	Cancer, neurodegeneration, sustained release
Dendrimers	Highly branched polymers	Tree-like structure, multiple cavities	Precise loading control, co-delivery capability	Curcumin, EGCG	Cancer (co-delivery), CNS disorders
Plant-derived Exosomes/EVs*	Plant cell membranes	Nano-sized vesicles (30–200 nm), natural lipid bilayers	Biocompatible, low immunogenicity, natural homing, oral stability	Curcumin, quercetin, ginger-derived compounds	Cancer, colitis, neurodegeneration
Hybrid Nanocarriers	Polymer-lipid or lipid-inorganic composites	Combined structural features of two or more systems	Synergistic benefits: improved solubility, targeting, prolonged circulation	Curcumin, resveratrol, EGCG	Precision medicine, complex chronic diseases

carry poorly soluble phytochemicals in hydrophobic cores, protecting them from premature degradation (Jacob et al., 2024).

4.4. Inorganic and metallic nanocarriers

Gold nanoparticles (AuNPs) provide surface modification capabilities and inherent imaging properties, making them effective theranostic nanocarriers for anticancer phytochemicals (Sargazi et al., 2022). EGCG and luteolin have been effectively conjugated with AuNPs for tumor targeting (Karimi-Shahri et al., 2023). Silver nanoparticles (AgNPs) amplify antimicrobial activity of plant-based compounds against resistant isolates (Anand et al., 2022). Mesoporous silica nanoparticles (MSNs) provide wide surface area and tunable pore size for high drug loading and precise release of phytochemicals in cancer and neurological diseases (Djayanti et al., 2023).

4.5. Dendrimers and hybrid nanocarriers

Dendrimers highly branched tree-like structures provide precise control over phytochemical loading and release through their multiple surface functionalities and internal cavities (Adnan Raza et al., 2025). Their structural versatility enables co-delivery of multiple phytochemicals or phytochemical-drug combinations for synergistic effects; dendrimer-based curcumin-doxorubicin co-delivery systems exemplify this approach in cancer therapy (Mahjubin-Tehran et al., 2024). Hybrid nanocarriers combining polymer-lipid, liposome-inorganic, or other composite architectures simultaneously confer improved solubility, extended circulation, enhanced specificity, and lower toxicity (Huang et al., 2024).

4.6. Emerging carriers: plant-derived exosomes and extracellular vesicles

A novel frontier in nanophytomedicine is the use of plant-derived exosomes and extracellular vesicles (EVs). These natural nano-sized vesicles (30–200 nm) derived from plant cells carry endogenous bioactive cargo including miRNAs, proteins, and phytochemicals in a natural lipid bilayer envelope. Plant-derived EVs exhibit inherent oral stability, low immunogenicity, and natural homing properties not found in synthetic nanocarriers. Ginger-derived EVs, for instance, have demonstrated anti-inflammatory and anti-colitis effects in preclinical models, while EVs from grapes and broccoli have shown selective tumor cell uptake. These vesicles can be loaded with exogenous phytochemicals including curcumin and quercetin, providing a fully biogenic delivery platform. Compared with synthetic liposomes, plant EVs offer superior biocompatibility, reduced manufacturing toxicity, and potential for large-scale extraction from agricultural sources. However, challenges remain in standardization of EV isolation methods, batch-to-batch reproducibility, and characterization of cargo loading efficiency. This represents a high-priority area for future research in the field.

5. Major phytochemicals used in nanoformulations

The therapeutic potential of phytochemicals has been extensively studied across cancer, diabetes, cardiovascular, and neurological diseases (Xavier et al., 2024). However, poor water solubility, rapid metabolic breakdown, physiological instability, and low oral absorption limit their clinical translation. Nanotechnology-based delivery systems consistently improve pharmacokinetic and targeting profiles of these compounds. Table 3 summarizes the major phytochemicals used in nanoformulations, while Tables 4 and 5 illustrate associated nanocarrier benefits and disease-specific applications.

5.1. Curcumin

Curcumin, turmeric's principal active ingredient, is well-known for anti-inflammatory, antioxidant, and anticancer properties but is rarely used clinically due to poor aqueous solubility, rapid elimination, and pH-dependent instability. Encapsulation in PLGA nanoparticles and lipid carriers enables targeted CNS delivery for Alzheimer's disease through amyloid-beta modulation (Shahbaz et al., 2022). Curcumin-loaded liposomes and micelles enhance tumor cell cytotoxicity with minimal damage to healthy tissues. Nanoformulations also enable sustained intracellular retention in inflamed tissues, extending

Table 3
Major phytochemicals in nanoformulations.

Phytochemical	Source	Key Biological Activities	Pharmacokinetic Limitations	Nanocarrier Strategies	Enhanced Therapeutic Applications
Curcumin	Curcuma longa (Turmeric)	Anti-inflammatory, antioxidant, anticancer, neuroprotective	Poor solubility, low absorption, instability at physiological pH, rapid elimination	Liposomes, PLGA NPs, SLNs, dendrimers, micelles	Alzheimer's disease (amyloid modulation), cancer (enhanced cytotoxicity), chronic inflammation (sustained anti-inflammatory action)
Resveratrol	Grapes, berries, peanuts	Cardioprotective, neuroprotective, anti-aging, anti-inflammatory	Poor solubility, rapid metabolism, photosensitivity	Chitosan NPs, PLGA NPs, lipid-based systems	Atherosclerosis (endothelial protection), neurodegenerative diseases (enhanced brain delivery), anti-aging therapy
Quercetin	Onions, apples, green tea	Antioxidant, anti-inflammatory, antidiabetic, anticancer	Poor solubility, rapid elimination, poor absorption	Micelles, nanoemulsions, polymeric NPs	Cancer (enhanced apoptosis), diabetes (better glycemic control), oxidative stress disorders (ROS modulation)
Berberine	Berberis vulgaris and other Berberis species	Antimicrobial, antidiabetic, anti-inflammatory, lipid-lowering	Low oral bioavailability, first-pass metabolism, P-gp efflux	SLNs, SEDDS, micelles, chitosan NPs	Type 2 diabetes (insulin sensitivity), metabolic syndrome (lipid profile modulation), gut microbiota regulation
EGCG	Green tea (Camellia sinensis)	Chemopreventive, cardioprotective, anti-obesity, anti-inflammatory	Poor stability (alkaline pH), low bioavailability, low membrane permeability	Lipid NPs, polymeric NPs, dendrimers	Cancer (pro-apoptotic effect), metabolic syndrome (reduced inflammation), obesity (weight reduction)
Kaempferol	Leafy greens, apples, tea	Antioxidant, anti-inflammatory, neuroprotective	Limited absorption, rapid metabolism	Polymeric NPs, nanoemulsions	Neurodegeneration, cardiovascular protection
Catechin	Green tea, cocoa, berries	Antioxidant, antidiabetic, cardioprotective	Low bioavailability, unstable in GI tract	Chitosan NPs, liposomes	Diabetes (glucose regulation), cardiovascular diseases
Naringenin	Citrus fruits (grapefruit, oranges)	Antioxidant, lipid-lowering, hepatoprotective	Poor water solubility, poor intestinal absorption	Polymeric NPs, nanoemulsions	Liver disorders, hyperlipidemia, metabolic syndrome
Silymarin	Milk thistle (Silybum marianum)	Hepatoprotective, antioxidant, antifibrotic	Low solubility, poor absorption, rapid metabolism	Micelles, SLNs, PEGylated NPs	Liver cirrhosis, hepatitis, detoxification
Apigenin	Parsley, chamomile, celery	Anti-inflammatory, anticancer, neuroprotective	Poor solubility, low systemic retention	PLGA NPs, lipid NPs	Cancer chemoprevention, neuroinflammation control
Thymoquinone	Black seed (Nigella sativa)	Antioxidant, anticancer, anti-inflammatory	Low solubility, instability, rapid metabolism	Lipid NPs, polymeric carriers	Cancer (apoptosis induction), inflammation (NF-κB modulation)

Table 4
Nanocarrier-enhanced benefits and therapeutic applications of major phytochemicals.

Nanocarrier Benefit	Explanation	Associated Phytochemicals	Enhanced Therapeutic Domains
Improved Solubility	Enhances dissolution rate of hydrophobic compounds	Curcumin, Quercetin, Silymarin, Thymoquinone	Cancer, Diabetes, Liver diseases
Enhanced Bioavailability	Increases systemic concentration and therapeutic index	EGCG, Berberine, Resveratrol	Cancer, Cardiovascular diseases, Metabolic syndrome
Protection from Degradation	Shields compounds from pH, enzymatic, and light-induced breakdown	Resveratrol, EGCG, Quercetin	Neurodegeneration, Cancer, Inflammation
Controlled and Sustained Release	Ensures prolonged action at target site	Curcumin, Quercetin, Apigenin	Inflammatory diseases, Cancer
Targeted Delivery	Reduces off-target toxicity, increases accumulation at disease sites	Curcumin, EGCG, Apigenin	Cancer, Inflammation, Neurodegeneration
Crossing Biological Barriers	Facilitates penetration across barriers like the blood–brain barrier (BBB)	Curcumin, Resveratrol, EGCG	Neurodegeneration (Alzheimer's, Parkinson's)
Reduced Systemic Toxicity	Minimizes off-target drug exposure through site-specific delivery	Thymoquinone, Berberine, Quercetin	Cancer, Metabolic disorders
Co-delivery Capability	Enables simultaneous loading of phytochemicals and/or synthetic drugs	Curcumin + doxorubicin, EGCG + cisplatin	Multidrug-resistant cancer, Metabolic syndrome

Table 5
Targeted therapeutic applications of nanoformulated phytochemicals across major disease areas.

Disease Area	Key Phytochemicals	Nanoformulation Strategies	Linked Nanocarrier Benefits	Nano-Enabled Therapeutic Advantage
Cancer	Curcumin, EGCG, Quercetin, Apigenin, Resveratrol	Liposomes, Micelles, Dendrimers, Gold NPs, PLGA NPs	Improved solubility, targeted delivery, controlled release, MDR reversal	EPR-based and ligand-targeted tumor accumulation
Neurodegeneration (Alzheimer's, Parkinson's)	Resveratrol, Curcumin, EGCG, Kaempferol	PLGA NPs, Lipid-based NPs, PEGylated carriers, Dendrimers	BBB penetration, protection from degradation, sustained release	Enhanced brain bioavailability, reduced peripheral toxicity
Cardiovascular Diseases	Resveratrol, Catechin, Kaempferol, Quercetin, Berberine	Polymeric NPs, Lipid NPs, Chitosan NPs	Enhanced bioavailability, antioxidant delivery, targeted vascular action	Reduced atherosclerotic progression, improved endothelial function
Diabetes & Metabolic Syndrome	Berberine, Quercetin, EGCG, Naringenin, Curcumin	SEDDS, SLNs, Nanoemulsions, Polymeric NPs	Improved solubility, intestinal retention, systemic availability	Enhanced insulin sensitivity, improved glycemic and lipid control
Liver Diseases	Silymarin, Thymoquinone, Curcumin	Micelles, PEGylated NPs, Nanoemulsions	Improved bioavailability, hepatoprotection, liver-targeted delivery	Protection from first-pass metabolism, hepatic regeneration
Inflammatory Diseases	Curcumin, Apigenin, Thymoquinone, EGCG	Sustained-release polymeric/lipid systems, Dendrimers	Anti-inflammatory targeting, prolonged effect, reduced toxicity	Site-specific cytokine suppression, corticosteroid-sparing potential

anti-inflammatory activity (Jacob et al., 2024; Yallapu et al., 2015).

5.2. Resveratrol

Resveratrol, a polyphenolic stilbene found in grapes and berries, has cardiovascular, neuroprotective, and anti-aging properties limited by low solubility, rapid hepatic metabolism, and light sensitivity (Bejenaru et al., 2024). Nanoencapsulation in chitosan, PLGA, and lipid-based systems greatly enhances its stability and bioavailability. Nano-resveratrol formulations cross the blood-brain barrier and increase brain drug concentration for diseases such as Parkinson's and Alzheimer's, while tissue-specific targeting reduces systemic side effects (Salla et al., 2024).

5.3. Quercetin

Quercetin is a flavonoid with powerful antioxidant, anti-inflammatory, antidiabetic, and anticancer activities whose clinical use is limited by poor water solubility and rapid elimination (Azeem et al., 2023). Packaging with micelles, nanoemulsions, and polymeric nanoparticles enhances cancer cell apoptosis induction and sustained delivery. In diabetes, nanocarriers improve intestinal absorption and slow release, enhancing glycemic control and pancreatic protection (Alharbi et al., 2025; Singh et al., 2018).

5.4. Berberine

Berberine, from Berberis vulgaris, has significant antimicrobial, antidiabetic, and metabolic benefits but is poorly absorbed due to low intestinal permeability, rapid first-pass metabolism, and P-glycoprotein efflux (Mujtaba et al., 2022). Solid lipid nanoparticles, SEDDS, and polymeric micelles enhance intestinal retention and cellular permeability. Nano-berberine improves lipid profiles, insulin sensitivity, and inflammatory markers in metabolic syndrome and type 2 diabetes (Mohammadzadeh et al., 2024).

5.5. EGCG and other polyphenols

Epigallocatechin-3-gallate (EGCG) from green tea is well documented for chemopreventive, cardioprotective, and metabolic health benefits, but is unstable in alkaline settings with low membrane permeability and bioavailability (Capasso et al., 2025). Nanoformulated EGCG enhances anticancer efficacy by regulating cell growth, apoptosis, and angiogenesis (Shabana et al., 2024). EGCG nanoformulations also reduce weight, improve insulin sensitivity, and exert anti-inflammatory effects in metabolic syndrome. Other phytochemicals kaempferol, catechin, naringenin, silymarin, apigenin, and thymoquinone similarly benefit from nanoencapsulation that enhances bioavailability and chronic disease efficacy as summarized in Table 3.

6. Nano-enhanced phytomedicine for specific chronic diseases

Nanotechnology in phytomedicine has expanded therapeutic possibilities for chronic diseases by addressing limitations of traditional phytochemicals including poor targeting, high off-target toxicity, and rapid elimination. Nano-modified phytochemicals are more effective because they improve absorption, biodistribution, sustained delivery, and tissue-specific accumulation, as illustrated in Table 6.

6.1. Cancer

Cancer remains a leading cause of death globally. Phytochemicals fight tumors through cell cycle arrest, apoptosis induction, angiogenesis inhibition, and signaling pathway modulation. However, poor solubility, short half-life, and insufficient tumor localization restrict clinical application. Nanocarrier systems address these limitations: curcumin delivered via liposomes or gold nanoparticles selectively accumulates in tumor tissues through the EPR effect, inducing apoptosis and minimizing damage to healthy cells. Co-delivery of phytochemicals with chemotherapeutic drugs in a single nanocarrier system provides synergistic effects and overcomes multidrug resistance (Gao et al., 2022). EGCG–chitosan nanoparticle systems modulate oncostatic signaling pathways in hepatocellular carcinoma (Shabana et al., 2024). Quercetin-loaded nanoparticles promote cancer cell apoptosis with improved tumor specificity (Singh et al., 2025).

6.2. Neurodegenerative diseases

Neurodegeneration including Alzheimer's and Parkinson's disease – is characterized by neuronal loss, oxidative stress, neuroinflammation, and pathological protein aggregation (Teleanu et al., 2022). The blood-brain barrier (BBB) presents a formidable challenge for CNS drug delivery (Wu et al., 2023). Polymeric nanoparticles, lipid-based systems, and dendrimers loaded with resveratrol, curcumin, and EGCG penetrate the BBB by evading efflux pumps and enzymatic degradation, enabling sustained brain-targeted release (Mishra et al., 2023; Rassu et al., 2023). These nanoformulations inhibit amyloid-beta and alpha-synuclein aggregation, scavenge ROS, and suppress neuroinflammation via Nrf2 and TNF-alpha modulation. De Lima et al. (2025) reviewed polyphenol, alkaloid, and terpenoid nanoformulations with established neuroprotective activity, highlighting their promise in clinical translation.

6.3. Cardiovascular diseases

Cardiovascular diseases (CVDs) including atherosclerosis, hypertension, and heart failure are driven by chronic inflammation, oxidative stress, and dyslipidemia (Frąk et al., 2022). Quercetin, resveratrol, and berberine improve vascular function, reduce lipid levels, and attenuate inflammatory and oxidative damage. Their clinical utility is limited by low bioavailability and rapid degradation. PLGA nanoparticles loaded with resveratrol boost endothelial nitric oxide production and reduce inflammation, improving vascular function and reducing plaque formation (Pechanova et al., 2020). Lipid-based nanoparticles carrying quercetin or EGCG stabilize atherosclerotic lesions, lower LDL oxidation, and improve cardiac function (Sharma and Sharma, 2022).

6.4. Diabetes and metabolic syndrome

Diabetes mellitus and metabolic syndrome are characterized by insulin resistance, chronic inflammation, and poor glucose metabolism (Fahed et al., 2022). Berberine, quercetin, curcumin, and EGCG affect insulin sensitivity, reduce blood glucose, and improve lipid profiles, but are hampered by poor GI absorption and rapid breakdown. Nano-berberine preparations improve gut absorption and reduce blood glucose more effectively than conventional berberine in animal models (Mirhadi et al., 2018). Curcumin-loaded PLA-PEG nanoparticles enhanced insulin sensitivity and decreased hepatic glucose production in diabetic rats (El-Naggar et al., 2019). Nanoformulations also enable targeted gut delivery of berberine, supporting gut microbiota regulation and metabolic improvements (Uti et al., 2025).

6.5. Liver and inflammatory diseases

Liver diseases including NAFLD and hepatitis are addressable by silymarin, thymoquinone, and curcumin through hepatocyte protection, antioxidant enzyme activation, and anti-fibrotic effects. PEGylated nanoparticles and nanoemulsions protect these compounds from first-pass metabolism and improve liver-targeting efficiency. In

Table 6
Nano-enhanced phytomedicine for specific chronic diseases.

Chronic Disease	Key Phytochemicals	Nanocarrier Strategies	Mechanisms of Action	Nano-Enabled Therapeutic Advantages
Cancer	Curcumin, EGCG, Quercetin, Apigenin, Resveratrol	Liposomes, Gold NPs, Dendrimers, PLGA NPs, Micelles	Induction of apoptosis; inhibition of angiogenesis and proliferation; modulation of NF-κB, PI3K/Akt, MAPK pathways	Tumor-targeted delivery via EPR and ligand-based targeting; improved solubility and bioavailability; reduced systemic toxicity; overcoming multidrug resistance through co-delivery
Neurodegenerative Diseases (Alzheimer's, Parkinson's)	Curcumin, Resveratrol, EGCG, Kaempferol	PLGA NPs, Lipid-based NPs, Dendrimers, PEGylated carriers	Inhibition of amyloid-β/α-synuclein aggregation; ROS scavenging and antioxidant effects; neuroinflammation suppression via Nrf2, TNF-α modulation	Effective BBB penetration; sustained brain-targeted release; reduced peripheral exposure; enhanced neuroprotection and synaptic function
Cardiovascular Diseases (CVDs)	Resveratrol, Quercetin, EGCG, Berberine	Polymeric NPs, Lipid NPs, Chitosan NPs	Enhancement of endothelial nitric oxide production; inhibition of LDL oxidation and foam cell formation; anti-inflammatory and antioxidant effects via Nrf2 and HO-1 pathways	Targeted vascular delivery; stabilization of atherosclerotic plaques; controlled and sustained drug release; improved cardiac function with fewer side effects
Diabetes & Metabolic Syndrome	Berberine, Curcumin, EGCG, Quercetin, Naringenin	SLNs, Nanoemulsions, SEDDS, Polymeric NPs	Modulation of insulin signaling (PI3K/Akt pathway); reduction of glucose absorption and hepatic gluconeogenesis; enhancement of GLUT4 translocation; lipid profile normalization	Increased intestinal absorption; protection from enzymatic degradation; enhanced hypoglycemic and insulin-sensitizing effects; reduced dosing frequency and improved compliance
Inflammatory & Autoimmune Disorders	Curcumin, Apigenin, Thymoquinone, EGCG	Sustained-release systems, Lipid NPs, Dendrimers	Downregulation of pro-inflammatory cytokines (IL-6, TNF-α); NF-κB inhibition; suppression of COX-2 and iNOS expression	Site-specific delivery to inflamed tissues; prolonged anti-inflammatory effect; reduced gastrointestinal side effects; potential corticosteroid-sparing effects
Liver Diseases (NAFLD, Hepatitis)	Silymarin, Thymoquinone, Curcumin	PEGylated NPs, Micelles, Nanoemulsions	Hepatocyte protection via antioxidant enzyme activation; reduction in liver transaminases and fibrosis markers; anti-fibrotic and regenerative effects	Enhanced liver-targeting efficiency; protection from first-pass metabolism; improved therapeutic index and safety profile

Table 7
Novelty comparison of this review against key representative published reviews.

Reference	Topic	Focus Area	Gap Identified	How This Review Adds Novelty
Gao et al. (2022)	Co-delivery nanomedicine for phytochemicals + chemo	Cancer co-delivery via nanomedicines	Cancer-focused; no systematic disease comparison	Our review covers 6 chronic disease domains; includes EVs/exosomes; comparative disease-specific mechanism tables (Tables 4–6)
Elmowafy et al. (2023)	Polymeric NPs for bioactive agents	Polymeric NP platform review	Limited to polymeric carriers; no disease-specific mapping	Our review integrates 8 nanocarrier classes across disease targets with mechanistic analysis
Kothapalli and Vasanthan (2024)	Lipid-based NCs for plant bioactives	Lipid carrier systems	Lipid-centric; excludes inorganic/hybrid carriers	We include metallic NPs, MSNs, hybrid systems, and emerging EVs not covered in lipid-only reviews
Chauhan et al. (2024)	Nanotechnology for phytochemical delivery	Broad nanotech for phytochemicals	Limited methodology; no systematic search reporting	Our review provides full PRISMA-inspired methodology, search syntax, and novelty comparison table
Razavi et al. (2024)	Herbal cancer nanomedicine review	Cancer-focused phyto-nanomedicine	Restricted to cancer; no CVD/ neurodegeneration coverage	We comprehensively cover cancer, neurodegeneration, CVD, diabetes, liver, and inflammatory diseases
Teli et al. (2024)	Phytochemical-nanotech convergence	General phyto-nanotech overview	No quantitative synthesis; limited mechanistic depth	Our mechanistic tables and emerging carrier sections (EVs, green synthesis, AI-assisted design) add new analytical depth

inflammatory and autoimmune disorders, site-specific delivery of curcumin, apigenin, and thymoquinone via sustained-release polymer-lipid systems down-regulates IL-6, TNF-alpha, NF-kappaB, COX-2, and iNOS expression with prolonged anti-inflammatory effects and reduced gastrointestinal side effects.

7. Advantages and limitations of nano-phytomedicine

Nano-phytomedicine offers substantial advantages over conventional phytochemical delivery. Bioavailability enhancement is paramount: liposomes, polymeric nanoparticles, and SLNs allow the body to absorb poorly soluble compounds such as curcumin, resveratrol, and quercetin more effectively and sustain them in the bloodstream (Awlqadr et al., 2025; Chauhan et al., 2024). Nanocarriers prevent premature gastrointestinal degradation and pH-induced inactivation. Targeted delivery through ligand-functionalized nanocarriers (antibodies, peptides, small molecules) reduces off-target effects and accumulates drugs at pathological sites (Omidian et al., 2025). Controlled and sustained release maintains stable drug concentrations, reducing dosing frequency and improving chronic disease management (Mbata et al., 2024). For cancer and neurological diseases, nanoformulations cross critical biological barriers including the BBB and the tumor microenvironment (Rassu et al., 2023). Co-delivery of phytochemicals with synthetic drugs enables synergistic therapy with reduced drug resistance.

Limitations are equally significant. Nanotoxicity concerns persist: while PLGA and lipid-based systems are FDA-approved, metallic nanoparticles may cause cytotoxicity, oxidative stress, and immunogenicity depending on size, surface charge, and composition as shown in Fig. 2 (Yusuf et al., 2023). Long-term organ accumulation and biodegradation products require extensive in vivo safety profiling (Ajdary et al., 2018). Formulation stability – including aggregation, drug leakage, and storage degradation complicates manufacturing and clinical use. Industrial-scale production with reproducible particle size and encapsulation efficiency demands stringent quality control. Regulatory frameworks for nano-phytomedicines remain fragmented: the FDA and EMA lack unified guidelines for herbal-based nanomedicines (Đorđević et al., 2022). High development costs and complex IP landscapes further constrain commercialization, particularly in low- and middle-income countries (Sawhney et al., 2020).

8. Clinical studies and translational potential

The clinical translation of nano-phytomedicine is advancing, with growing preclinical and clinical evidence supporting efficacy and safety. Nanoformulated phytochemicals consistently demonstrate superior pharmacological activity compared to conventional phytochemicals through enhanced solubility, bioavailability, and selective distribution

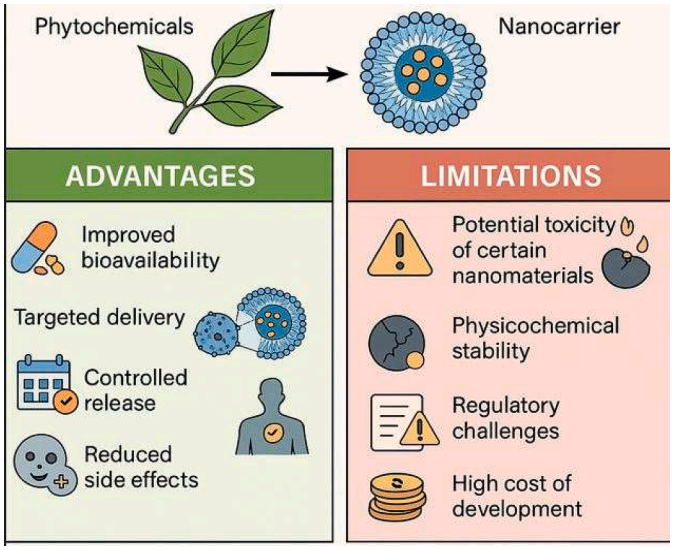


Fig. 2. Advantages and limitations of nano-phytomedicine.

as shown in Fig. 3 (Petrovic et al., 2024). Liposomal curcumin has advanced to Phase I clinical trials in cancer patients and has demonstrated safety and tolerability at therapeutic doses. Polymeric nanoparticles containing berberine are under development for metabolic syndrome and Type 2 diabetes. Nano-emulsified formulations of EGCG and resveratrol are being investigated as antioxidant and anti-inflammatory agents in cardiovascular and neurological diseases (Jangid and Sharma, 2025).

Translational challenges are substantial. Phytochemicals vary naturally based on species, cultivation conditions, and extraction techniques, complicating quality standardization (Mutha et al., 2025). Nanocarrier systems add analytical complexity requiring specialized validation methods for particle size, surface charge, drug loading, stability, and biological interactions not covered by standard herbal medicine frameworks (Khan et al., 2025). Long-term safety, biodistribution, and nanotoxicity profiling require extensive follow-up (Ahmad et al., 2022). Industrial manufacturing with batch-to-batch homogeneity, stability, and cost-effectiveness is technically demanding (Fernandes et al., 2023; Liu and Meng, 2021). Standardization of phytochemical and nanocarrier components, combined with the environmental sensitivity of nanoformulations, results in shelf-life and clinical application challenges (Naik et al., 2023). Despite these barriers, collaborative efforts among researchers, industry, and regulatory agencies are narrowing the gap between laboratory achievements and clinical application.

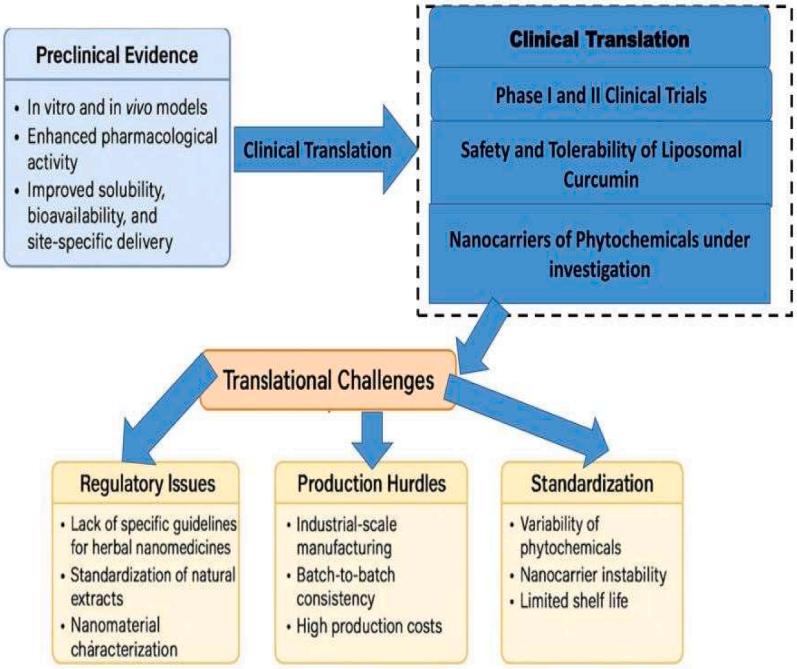


Fig. 3. Clinical studies and translational potential.

9. Future perspectives and research directions

Future nano-phytomedicine research will move toward individualized, sustainable, and integrative therapeutic approaches. Personalized nanophytomedicine integrating patient-specific genetic, metabolic, and disease variables with genomic sequencing and biomarker profiling – will allow development of nanoformulations tailored to individual differences in drug metabolism and disease progression (Chattopadhyay et al., 2025). Ligand-functionalized personalized delivery systems will enable highly specific drug delivery to diseased cells with minimal off-target effects (Mitchell et al., 2021).

Green nanotechnology and biogenic nanoparticles synthesized from plant extracts or microorganisms represent a major growth area (Hano and Abbasi, 2021). These approaches decrease hazardous chemical requirements in nanoparticle production while introducing the natural bioactivity of plant components into the nanostructure itself. Green synthesis methods are economical, scalable, and sustainable, making them particularly attractive in resource-limited settings. Further research should focus on simplifying biogenic production processes and improving characterization of resultant nanoparticles.

The combination of nano-phytomedicine with conventional pharmaceuticals offers synergistic therapeutic effects, reduced drug resistance, and enhanced outcomes (Mosoh, 2025). Co-encapsulation of chemotherapeutic agents with plant-derived antioxidants enhances tumor cell killing while reducing systemic oxidative stress and chemotherapy toxicity (Razavi et al., 2024). AI-assisted nanoformulation design is an emerging frontier: machine learning algorithms can predict optimal nanocarrier composition, particle size, and surface chemistry for specific phytochemical-disease combinations, accelerating formulation development and reducing experimental burden.

Long-term safety and efficacy studies in human populations remain an urgent priority, as most evidence derives from short-term in vitro or animal studies. Biodistribution, organ accumulation, degradation, and immunogenicity must be studied through extensive longitudinal clinical trials, particularly for lifelong conditions. Harmonized regulatory frameworks for herbal-based nanomedicines addressing standardization, quality assurance, and ethical issues are essential to enable clinical translation.

10. Conclusion

Nanocarrier technology has transformed the therapeutic potential of plant-based medicines for chronic disease management. Liposomes, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions, micelles, metallic nanostructures, plant-derived exosomes, and hybrid systems have all been demonstrated to improve the pharmacokinetic and pharmacodynamic profiles of bioactive phytochemicals. Nanocarriers improve pharmaceutical performance and tolerability through controlled delivery, enhanced solubility, protection from degradation, and specific organ or cellular targeting. Nano-phytomedicines effectively overcome critical biological barriers including the blood-brain barrier and the dense tumor microenvironment, enhancing localized therapeutic effects while reducing systemic toxicity.

Despite these advances, major challenges remain. The failure to translate preclinical successes into clinical practice is a persistent concern, driven by insufficient long-term clinical data, absence of standardization of nanocarrier production and dosing, nanotoxicity concerns, and a fragmented regulatory landscape for herbal nanomedicine. Addressing these obstacles requires multidisciplinary collaboration across nanotechnology, pharmacognosy, materials science, and clinical medicine. Large-scale multicentric clinical studies, green nanotechnology innovation, AI-assisted formulation design, and harmonized regulatory frameworks will collectively determine the future of nano-phytomedicine as a mainstream therapeutic modality. With continued scientific rigor and translational effort, nano-enhanced phytomedicine offers a safer, more effective, and comprehensive solution for chronic disease management globally.

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Declaration of competing interest

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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