

Nanotechnology in Herbal Drug Delivery: *Nanoformulations, Extraction Strategies, and Therapeutic Applications*

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Date of Submission: 12-05-2026

Date of Acceptance: 27-05-2026

Abstract

Nanotechnology has emerged as a transformative approach in herbal drug delivery, bridging traditional medicine with modern pharmaceutical science. Herbal extracts, long valued in Ayurveda, Traditional Chinese Medicine, and other indigenous practices, often suffer from poor solubility, instability, and limited bioavailability. Nanoformulations — such as polymeric nanoparticles, liposomes, nanoemulsions, nanomicelles, and dendrimers — address these challenges by enhancing solubility, improving stability, enabling controlled release, and facilitating targeted delivery.

Evidence from recent studies demonstrates significant improvements in pharmacokinetics and therapeutic efficacy of herbal bioactives including curcumin, quercetin, resveratrol, silymarin, and berberine when encapsulated in nanocarriers. These systems not only enhance oral bioavailability but also enable crossing of biological barriers such as the blood-brain barrier (BBB), opening avenues for neuroprotective and anticancer applications. Furthermore, advanced extraction technologies including ultrasound-assisted, enzyme-assisted, and supercritical fluid extraction ensure high-quality herbal inputs for nanoformulation.

Despite promising preclinical outcomes, challenges remain in standardization, regulatory approval, and clinical translation. Emerging trends such as stimuli-responsive nanocarriers, biomimetic systems, and artificial intelligence-driven formulation design are expected to accelerate innovation and clinical adoption. This comprehensive review highlights the evolution, strategies, advantages, and therapeutic applications of nanotechnology in herbal drug delivery, underscoring its potential to transform traditional remedies into evidence-based, clinically viable therapeutics.

Keywords: Nanotechnology, Herbal Medicine, Nanoformulations, Polymeric Nanoparticles, Drug Delivery, Bioavailability, Targeted Therapy, Artificial Intelligence

I. Introduction

1.1 Definition of Nanotechnology in Pharmacy

Nanotechnology in pharmacy refers to the application of nanoscale science and engineering to develop drug delivery systems that improve therapeutic efficacy, safety, and patient compliance. At the nanoscale (1–100 nm), materials exhibit unique physicochemical properties such as increased surface area, altered solubility, and enhanced permeability — properties fundamentally different from those of the same materials in bulk form. [1]

In herbal medicine, nanotechnology addresses challenges that have persisted for decades: poor aqueous solubility, chemical and environmental instability, and inconsistent bioavailability across patient populations. By encapsulating herbal extracts into nanoparticles, researchers achieve controlled release, targeted delivery, and improved pharmacokinetics. The outcome is a drug delivery platform where the ancient intelligence of botanical medicine is translated into rigorously reproducible, clinically effective formulations. [2,3]

The World Health Organization (WHO) estimates that approximately 80% of the global population relies on herbal medicines as part of their primary healthcare. Nanotechnology provides the bridge between traditional use and evidence-based clinical practice. [4]

1.2 Background

Herbal medicines have been integral to healthcare systems for centuries, particularly in Ayurveda, Traditional Chinese Medicine (TCM), and other indigenous practices. Ancient texts such as the Charaka Samhita and Huangdi Neijing documented the therapeutic potential of plant-based remedies with remarkable clinical sophistication. [5]

Conventional preparations — decoctions, tinctures, powders — while effective in historical contexts, lack the pharmacokinetic optimization required by modern clinical standards. Nanotechnology offers a transformative solution by reengineering these extracts into precisely defined

nanostructures. When curcumin is encapsulated in a polymeric nanoparticle, it is no longer merely a spice derivative but a pharmaceutical-grade therapeutic candidate with defined particle size, surface charge, release kinetics, and bioavailability profile. [16,42]

1.3 Role of Nanotechnology in Drug Delivery

Nanotechnology plays a transformative role in modern drug delivery by enabling precise, efficient, and targeted therapeutic approaches. Targeted delivery is perhaps the most celebrated benefit: nanocarriers can be surface-functionalized

with ligands, antibodies, or aptamers that specifically bind to receptors overexpressed on diseased cells, particularly cancer cells. [3,42]

For poorly soluble drugs — which constitute approximately 40% of marketed drugs and over 70% of compounds in the drug development pipeline — nanoencapsulation dramatically improves apparent solubility and dissolution rate. Furthermore, nanotechnology enables drugs to cross biological barriers such as the blood-brain barrier (BBB), opening therapeutic possibilities for neurological disorders. [4,19]

Table 1: Conventional vs. Nanotechnology-Based Drug Delivery — Comparative Overview

S.No	Feature	Conventional Delivery	Nanotechnology-Based Delivery	Reference
1	Drug Solubility	Limited for hydrophobic drugs	Enhanced via nanoformulations	[3]
2	Targeting Ability	Non-specific, systemic	Site-specific, receptor-mediated	[3]
3	Release Profile	Immediate or uncontrolled	Controlled, sustained release	[19]
4	Side Effects	Higher due to systemic spread	Reduced via targeted action	[4]
5	Barrier Penetration	Often restricted	Can cross BBB and mucosal barriers	[4]

Table 1: Comparative overview — conventional vs. nanotechnology-based drug delivery systems. [3,4,19]

1.4 Why Are Nanoformulations Important?

Nanoformulation represents a breakthrough in modern drug delivery. From a solubility standpoint, drugs that are poorly soluble or unstable in traditional forms can be encapsulated in nanoparticles, improving absorption and therapeutic effectiveness. Stability represents another compelling reason for nanoformulation adoption — the lipid nanoparticle (LNP) technology enabled the rapid development of mRNA vaccines during the COVID-19 pandemic and is now being investigated for CRISPR gene editing delivery. [5,7,19]

1.5 Historical Perspective of Herbal Medicines

Herbal medicines have been used for millennia, forming the backbone of traditional healthcare systems such as Ayurveda, Traditional Chinese Medicine, and Unani. The 20th century saw a critical bifurcation in medicine, but the late 20th and early 21st centuries saw a renaissance: epidemiological studies confirmed the efficacy of many traditional botanicals, genomic tools allowed identification of their bioactive mechanisms, and nanotechnology provided the delivery infrastructure to make them clinically competitive. [8,9]

Table 2: Timeline of Nanoformulations in Herbal Drug Delivery

S.No	Period	Key Developments	Reference
1	Pre-20th C.	Herbal medicines in Ayurveda, TCM, Unani. Delivery was crude (powders, decoctions, tinctures) with poor bioavailability.	[8,9]
2	1970s–1980s	Emergence of nanotechnology in medicine. Liposomes introduced as drug carriers, laying the foundation for herbal nanoformulations.	[10]
3	1990s	First attempts to encapsulate herbal bioactives (curcumin, silymarin) in liposomes and polymeric nanoparticles.	[11]

S.No	Period	Key Developments	Reference
4	2000–2010	Growth of solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanoparticles applied to herbal extracts.	[12]
5	2010–2015	Rise of nanoemulsions, nanogels, phytosomes for quercetin, resveratrol, curcumin. Enhanced absorption reported.	[16]
6	2015–2020	Targeted nano-herbal formulations using ligands, antibodies, stimuli-responsive systems. Applications expanded to cancer, neuroprotection, dermatology.	[13]
7	2020–Present	Integration of green nanotechnology, hybrid nanocarriers, and AI/computational modelling. Focus on clinical translation and regulatory frameworks.	[1,2,14]

Table 2: Timeline of nanoformulations in herbal drug delivery systems. [1,2,8,10,11,12,13,14,16]

III. Nanoformulation Strategies in Drug Delivery

Nanoformulation strategies are innovative approaches in pharmaceutical science that use nanotechnology to design drug delivery systems. The diversity of available nanocarrier platforms allows formulation scientists to match the specific physicochemical and biological requirements of each herbal extract to the most appropriate carrier system. [3,16,19]

3.1 Polymeric Nanoparticles

Polymeric nanoparticles are among the most versatile and extensively studied nanocarrier systems. Drugs are encapsulated within a polymer matrix — commonly poly(lactic-co-glycolic acid) (PLGA), chitosan, or albumin — forming spherical particles in the 100–500 nm range. The biodegradable nature of these polymers enables controlled and sustained delivery profiles. [15,16]

For herbal compounds, polymeric nanoparticles offer particular benefits in overcoming first-pass metabolism. Encapsulation within PLGA or chitosan matrices protects herbal bioactives like berberine and curcumin from gastrointestinal degradation and facilitates lymphatic uptake. Surface modification with polyethylene glycol (PEG) further extends circulation half-life by reducing opsonization and macrophage clearance. [17,18]

3.2 Liposomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core. Their structural amphiphilicity makes them uniquely versatile: hydrophilic drugs can be trapped in the aqueous

interior, while hydrophobic compounds are incorporated within the lipid bilayer. Several liposomal drug products are now established in clinical practice, including Doxil (liposomal doxorubicin) for cancer and AmBisome (liposomal amphotericin B) for fungal infections. [20,21]

In herbal medicine, liposomal silymarin and liposomal curcumin formulations have demonstrated significantly improved hepatoprotective and anti-inflammatory effects. The development of phytosomes — in which herbal bioactives are chemically complexed with phospholipids — further enhances gastrointestinal absorption. [22,23]

3.3 Nanoemulsions

Nanoemulsions are thermodynamically or kinetically stable dispersions of oil and water with droplet sizes typically in the 20–200 nm range. Their nano-scale droplet size provides a large interfacial area for drug dissolution and absorption, making them particularly effective for lipophilic herbal compounds. In topical and dermatological applications, nanoemulsions significantly enhance skin penetration by overcoming the stratum corneum barrier. [24,25]

3.4 Nanomicelles

Nanomicelles are self-assembled nanostructures formed by amphiphilic molecules above a critical micelle concentration. The hydrophobic core provides a reservoir for poorly water-soluble drugs, while the hydrophilic shell ensures water dispersibility and colloidal stability. Their compact size (10–100 nm) and minimal surface immunogenicity make them attractive for intravenous delivery and tumor targeting via the

enhanced permeability and retention (EPR) effect. [26,27]

3.5 Dendrimers

Dendrimers are highly branched, tree-like nanostructures. PAMAM (polyamidoamine) dendrimers are the most extensively studied class.

In herbal nanotechnology, dendrimers offer the unique capability of covalently conjugating herbal bioactives to the dendrimer surface or encapsulating them within internal cavities, enabling truly multifunctional theranostic systems. [28]

Table 3: Summary of Nanoformulation Strategies in Herbal Drug Delivery

S.No	Strategy	Description	Advantages	Examples	Reference
1	Polymeric NPs	Drugs in polymeric, lipid, or inorganic matrix	Enhanced stability, controlled release, targeted delivery	PLGA NPs, chitosan NPs	[15,16]
2	Liposomes	Spherical vesicles with phospholipid bilayers	Biocompatible; carries hydrophilic & hydrophobic drugs	Doxil (liposomal doxorubicin)	[20,21]
3	Nanomicelles	Amphiphilic molecules forming micelles	Solubilize poorly soluble drugs, EPR targeting	Paclitaxel micelles, berberine micelles	[26,27]
4	Dendrimers	Branched nanostructures with functional groups	High drug payload, surface modification possible	PAMAM dendrimers	[28]
5	Nanoemulsions	Oil-in-water or water-in-oil emulsions (20–200 nm)	Improve solubility, fast absorption, skin penetration	Herbal extract nanoemulsions	[24,25]
6	Polymeric Nanocarriers	Biodegradable polymers for sustained release	Tunable degradation, reduced toxicity	PLGA-based systems	[15,17]

Table 3: Major nanoformulation strategies in herbal drug delivery. [15,16,17,18,20,21,22,23,24,25,26,27,28]

IV. Advantages of Nano-Formulated Herbal Extracts

4.1 Enhanced Solubility and Bioavailability

Many herbal compounds are poorly soluble in water — a property that severely limits their absorption from the gastrointestinal tract. Curcumin is practically insoluble in water at physiological pH, and conventional preparations achieve negligible plasma concentrations after oral administration. PLGA nanoparticles have been shown to increase oral bioavailability in Wistar rats by up to 22-fold compared to unformulated curcumin, primarily by protecting the payload from gastric degradation and facilitating intestinal absorption. [29,30]

4.2 Improved Stability

Herbal extracts often degrade rapidly due to environmental factors — oxidation,

photodegradation, hydrolysis, pH changes, and enzymatic action. Phenolic compounds like resveratrol and EGCG are particularly vulnerable. Encapsulation in nanocarriers provides a protective shell that prevents direct contact between the active compound and degradative environmental agents, extending shelf life and maintaining potency. [19,31]

4.3 Controlled and Sustained Release

One of the most powerful capabilities of nanocarriers is their ability to modulate drug release kinetics. Through selection of polymer type, molecular weight, crystallinity, and crosslinking density, formulation scientists can engineer release profiles ranging from burst release for acute conditions to sustained release over days or weeks. Stimuli-responsive release — triggered by pH changes, temperature, redox gradients, or enzyme

activity — enables even more precise control. [32,33]

4.4 Targeted Delivery and Reduced Side Effects

Surface modifications on nanoparticles enable site-specific delivery to inflamed tissues, tumor cells, or specific organs. The concept of passive targeting via the EPR effect has been a cornerstone of cancer nanomedicine. Active targeting, achieved by conjugating targeting ligands (antibodies, aptamers, folate, transferrin) to the nanoparticle surface, adds an additional layer of specificity and reduces collateral damage to healthy tissues. [34,35]

4.5 Multifunctional and Cosmetic Applications

Nano-formulated herbal extracts demonstrate dual and even triple therapeutic action: cytotoxic activity

against cancer cells, antimicrobial effects against pathogens, and anti-inflammatory modulation — all from a single formulation platform. In cosmetic and dermatological applications, nanoemulsions and nanogels of herbal extracts penetrate deeper into skin layers, providing sustained hydration, UV protection, anti-aging effects, and depigmentation. [36,37]

V. Herbal Extracts in Nanoformulations

The following section provides a systematic overview of the most clinically significant herbal extracts investigated in nanoformulation systems, followed by detailed case studies. [3,16,38]

Table 4: Key Herbal Extracts and Their Nanoformulation Applications

S.No	Herbal Extract	Major Bioactives	Nanoformulation Type	Application/Outcomes	Reference
1	Curcumin (Turmeric)	Curcuminoids	NPs, nanoemulsions, liposomes	Anti-inflammatory, anticancer, improved bioavailability	[29,30,39]
2	Quercetin (Flavonoid)	Quercetin, Rutin, Isoquercitrin	Polymeric NPs, nanocapsules	Antioxidant, neuroprotective	[40,41]
3	Resveratrol (Grapes)	Resveratrol (stilbene polyphenol)	Nanogels, nanospheres	Anti-aging, cardioprotective	[43]
4	Aloe vera extract	Aloin, Emodin, Acemannan	Nanoemulsions, nanogels	Skin healing, anti-inflammatory	[44]
5	Neem (Azadirachta indica)	Azadirachtin, Nimbin, Gedunin	Nanoparticles, nanoemulsions	Antimicrobial, antifungal	[45,46]
6	Green tea (EGCG)	EGCG, Epicatechin gallate	Lipid nanoparticles	Anticancer, antioxidant	[47]
7	Ginseng extract	Ginsenosides (Rb1, Rg1, Re, Rd)	Nanocapsules	Immunomodulatory, anti-fatigue	[48]
8	Ashwagandha (W. somnifera)	Withanolides (Withaferin A)	Nanoparticles	Neuroprotective, adaptogenic	[49]

Table 4: Key herbal extracts and their nanoformulation applications. [29,30,39,40,41,43,44,45,46,47,48,49]

5.1 Case Studies

5.1.1 Curcumin (Turmeric)

Curcumin, the principal bioactive constituent of *Curcuma longa* (turmeric), exhibits anti-inflammatory mechanisms primarily through inhibition of NF- κ B signaling and cyclooxygenase enzymes, and anticancer properties through

induction of apoptosis, cell cycle arrest, and angiogenesis inhibition. Clinical translation has been severely hampered by poor aqueous solubility, rapid degradation at physiological pH, and extensive first-pass metabolism, resulting in bioavailability estimated at less than 1% in conventional oral formulations. [29,39]

Polymeric nanoparticles and nanoemulsions developed since 2020 have dramatically changed this picture. PLGA nanoparticles have been shown to increase oral bioavailability by up to 22-fold compared to unformulated curcumin. In vivo studies in xenograft mouse models have demonstrated tumor volume reductions exceeding 51% compared to equivalent doses of free curcumin, while inflammatory cytokine levels (TNF- α , IL-6) were significantly reduced. [30,50,51]

5.1.2 Quercetin (Flavonoid-Rich Plants)

Quercetin is a ubiquitous flavonoid found in onions, apples, berries, and many medicinal herbs. Its antioxidant capacity, anti-inflammatory properties, and emerging neuroprotective effects in models of Alzheimer's and Parkinson's disease have generated significant research interest. Quercetin's therapeutic potential is constrained by poor intestinal absorption — estimated at 17–25% in humans — and rapid phase II metabolism to glucuronide and sulfate conjugates that are pharmacologically inactive. [40,41]

Nanocapsule and nanogel formulations maintain plasma quercetin concentrations for substantially longer durations, critical for achieving neuroprotective effects. In Alzheimer's disease models, quercetin nanocapsules reduced oxidative stress markers (ROS, lipid peroxidation) by over 40%. [40,52]

5.1.3 Berberine (Ayurvedic Alkaloid)

Berberine is an isoquinoline alkaloid found in *Berberis vulgaris* and *Coptis chinensis* with roles in Ayurvedic and Traditional Chinese Medicine. P-glycoprotein efflux at the intestinal epithelium reduces oral bioavailability to approximately 5%. Lipid-based nanoparticles and nanomicelles address this pharmacokinetic barrier by facilitating lymphatic transport, bypassing hepatic first-pass metabolism, and inhibiting P-glycoprotein efflux. [53,54]

In antimicrobial studies, berberine nanomicelles have demonstrated 70% inhibition of biofilm formation in multi-drug resistant *Escherichia coli*. In metabolic disorder models, nano-berberine improved glycemic control by enhancing AMPK activation, with effects comparable to metformin at lower doses. [55,56]

5.1.4 Silymarin (Milk Thistle)

Silymarin is a complex of flavanolignans extracted from the seeds of *Silybum marianum* (milk thistle). Its hepatoprotective properties — well established

for liver cirrhosis, hepatitis, and toxic liver injury — are mediated through antioxidant, anti-inflammatory, and anti-fibrotic mechanisms. Conventional silymarin preparations achieve poor oral bioavailability (approximately 23–47%) due to low aqueous solubility and poor membrane permeability. [57,58]

Liposomes loaded with silymarin demonstrated 34-fold higher oral bioavailability compared to free silymarin, with increased hepatoprotective activity in CCl₄ and copper-induced liver injury models, alongside a significant decrease in ALT and AST liver enzyme levels. [57,59]

5.1.5 Neem and Tulsi Extracts

Neem (*Azadirachta indica*) and tulsi (*Ocimum sanctum*) are cornerstones of Ayurvedic medicine, revered for antimicrobial, anti-inflammatory, immunomodulatory, and wound-healing properties. Neem nanoemulsions inhibited *Candida albicans* growth by 80% compared to crude extracts. Tulsi nanogels accelerated wound closure in diabetic mice by 40% with concomitant reduction of inflammatory markers (IL-1 β , TNF- α) and enhanced epithelial regeneration. [45,46,60]

VI. Methods of Extraction of Herbal Bioactives

The quality and efficacy of any herbal nanoformulation is fundamentally determined by the quality of the herbal extract used as starting material. Extraction methodology governs the identity, purity, concentration, and stability of bioactive compounds in the extract. [61,62]

6.1 Conventional Extraction Methods

6.1.1 Maceration

Maceration is the simplest and oldest extraction technique, involving soaking plant material in a solvent at room temperature for an extended period with occasional agitation. While straightforward and inexpensive, maceration suffers from low efficiency for compounds tightly bound within plant cell matrices, and the prolonged extraction time increases the risk of microbial contamination and chemical degradation. [61]

6.1.2 Decoction

Decoction involves boiling plant material in water for a defined period. This technique is effective for extracting compounds from tough materials such as roots, bark, and seeds. However, the high temperatures involved preclude extraction of thermolabile compounds including volatile oils, many alkaloids, and heat-sensitive phenolics. [61]

6.1.3 Soxhlet Extraction

Soxhlet extraction, developed in 1879, remains

widely used for its ability to achieve exhaustive extraction through continuous solvent circulation. Limitations include long extraction times (4–48 hours), large solvent volumes, and potential thermal degradation of sensitive compounds during prolonged reflux. [62]

6.2 Modern and Advanced Extraction Methods

6.2.1 Ultrasound-Assisted Extraction (UAE)

Ultrasonic extraction harnesses the cavitation phenomenon to disrupt plant cell walls mechanically, facilitating rapid solvent penetration and release of bioactive compounds. Extraction times of 5–30 minutes routinely replace hours of conventional maceration with comparable or superior yields and reduced solvent consumption. UAE is highly scalable and has found widespread industrial adoption. [63,64]

6.2.2 Microwave-Assisted Extraction (MAE)

Microwave-assisted extraction uses microwave energy to heat solvents and plant tissue rapidly, generating high internal pressure within plant cells that ruptures cell walls and accelerates release of

bioactives. MAE achieves extraction times of minutes compared to hours for conventional methods, with high yields and significantly reduced solvent consumption. [64,65]

6.2.3 Enzyme-Assisted Extraction (EAE)

Enzyme-assisted extraction employs cellulases, pectinases, hemicellulases, and proteases to specifically degrade plant cell wall components, thereby releasing bioactive compounds from their structural matrix. EAE operates under mild aqueous conditions (30–50°C, physiological pH) and is environmentally friendly. [66]

6.2.4 Supercritical Fluid Extraction (SFE)

Supercritical fluid extraction uses carbon dioxide in its supercritical state (above 31°C and 74 bar) as the extraction solvent. After extraction, simple depressurization converts the supercritical CO₂ back to gas, leaving pure, solvent-free extract. SFE is uniquely suited to extraction of volatile oils, fat-soluble vitamins, cannabinoids, and other thermolabile lipophilic compounds. [67,68]

Table 5: Comparative Overview — Conventional and Modern Herbal Extraction Methods

S.No	Method	Principle	Speed/Yield	Advantages	Reference
1	Maceration	Room-temp solvent soaking	Slow/Moderate	Simple, inexpensive	[61]
2	Soxhlet	Continuous solvent reflux	Moderate/High	Exhaustive, reproducible	[62]
3	UAE	Ultrasonic cavitation	Fast/High	Less solvent, scalable	[63]
4	MAE	Microwave-driven heating	Very fast/High	Rapid, energy-efficient	[64,65]
5	EAE	Enzymatic cell wall breakdown	Moderate/High	Gentle, eco-friendly	[66]
6	SFE	Supercritical CO ₂ solubility	High/Selective	Solvent-free, green, high purity	[67,68]

Table 5: Comparative overview of conventional and modern herbal extraction methods. [61,62,63,64,65,66,67,68]

VII. Applications in Disease Management

7.1 Oncology and Cancer Therapy

Cancer represents arguably the most impactful application domain for herbal nanoformulations. Herbal bioactives such as curcumin, EGCG, berberine, and withanolides exhibit multi-target anticancer mechanisms (apoptosis induction, anti-angiogenesis, immunomodulation, chemosensitization) that complement conventional cytotoxic agents. Nanoparticle delivery of these

compounds to tumor tissue via EPR effect and active targeting dramatically improves tumor drug concentrations while sparing normal tissue. [69,70] Combination nanoformulations — encapsulating a herbal compound alongside a conventional chemotherapeutic agent — have shown synergistic cytotoxicity in preclinical models, suggesting potential for dose reduction of toxic synthetic drugs. [71,72]

7.2 Cardiovascular Disease

Cardiovascular disease remains the leading cause of global mortality. Herbal bioactives with documented cardiovascular benefits — resveratrol, quercetin, berberine, garlic organosulfur compounds — face significant bioavailability barriers that limit their clinical translation. Nanoformulation improves oral bioavailability, enabling effective plasma concentrations that correlate with demonstrated cardioprotective mechanisms: LDL oxidation inhibition, endothelial function improvement, platelet aggregation reduction, and anti-inflammatory action. [43,73]

7.3 Neurological Disorders

The blood-brain barrier (BBB) represents one of the most formidable obstacles in drug delivery. Nanotechnology offers several strategies to overcome this barrier: PEGylated nanoparticles exploit passive transport mechanisms, while receptor-mediated targeting using transferrin, insulin, or apolipoprotein E facilitates active transcytosis across the BBB. [4,74]

Herbal compounds with neuroprotective activity — ashwagandha withanolides for Alzheimer's protection, quercetin for oxidative stress reduction in Parkinson's models, berberine for neuroinflammation modulation — can be delivered to CNS targets via appropriate nanocarrier systems. [40,49,75]

7.4 Infectious and Antimicrobial Applications

The global antimicrobial resistance (AMR) crisis has renewed interest in natural antimicrobials as alternatives or adjuncts to conventional antibiotics. Herbal compounds such as berberine, neem azadirachtin, thymol, and carvacrol demonstrate activity against multi-drug resistant pathogens through mechanisms that differ fundamentally from conventional antibiotics. Silver nanoparticles biosynthesized using plant extracts demonstrate potent broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria, including MRSA and carbapenem-resistant Enterobacteriaceae. [55,56,76]

Table 6: Nanotechnology Applications in Disease Management

S.No	Application Area	Nanotech Role	Key Benefit	Example	Reference
1	Cancer	Targeted drug delivery	Reduced toxicity	Liposomal doxorubicin, curcumin NPs	[69,70]
2	Cardiovascular Disease	Imaging & nano-stents	Early detection, anti-restenosis	Magnetic NPs, resveratrol NPs	[43,73]
3	Infectious Disease	Antimicrobial coatings	Prevents resistance	Silver NPs, berberine nanomicelles	[55,56,76]
4	Neurological Disorders	BBB penetration	Effective CNS delivery	Nano-lipid carriers, quercetin NPs	[4,74,75]
5	Regenerative Medicine	Tissue scaffolds	Faster healing, epithelial regeneration	Nano-hydroxyapatite, tulsi nanogels	[60,77]

Table 6: Applications of nanotechnology-assisted herbal extracts in disease management. [4,43,55,56,60,69,70,73,74,75,76,77]

VIII. Challenges and Limitations

8.1 Scientific Challenges

8.1.1 Standardization of Herbal Extracts

Herbal extracts are inherently complex mixtures whose phytochemical compositions vary with plant species, geographic origin, cultivation conditions, harvest season, post-harvest handling, and extraction method. Regulatory agencies increasingly require standardization to specific marker compounds with defined concentration ranges. Developing validated

analytical methods for complex polyphytochemical matrices — using HPLC, LC-MS, NMR, DNA barcoding — is technically demanding and expensive. [78,79]

8.1.2 Stability of Nanoformulations

Nanocarriers including liposomes, polymeric nanoparticles, and nanoemulsions are thermodynamically metastable systems prone to aggregation, drug leakage, oxidative degradation, and polymer hydrolysis during storage. Strategies to

address stability include lyophilization with cryoprotectants, controlled packaging under nitrogen atmosphere, inclusion of antioxidants, and polymer surface modification. [79,80]

8.1.3 Bioavailability and Targeting Complexity

While nanoformulations generally improve bioavailability compared to conventional herbal preparations, achieving consistently predictable bioavailability in heterogeneous patient populations remains challenging. Active targeting approaches face complex *in vivo* challenges including protein corona formation on nanoparticle surfaces, heterogeneous receptor expression in tumors, and rapid nanoparticle clearance by the mononuclear phagocyte system. [80,81]

8.2 Technological Challenges

Transitioning from laboratory-scale synthesis (milligram quantities) to industrial production (kilogram to tonne scale) requires fundamentally different equipment and process engineering. Batch-to-batch consistency of nanoparticle size, size distribution, surface charge, drug loading, and encapsulation efficiency must be maintained across production scales. High-pressure homogenization, microfluidization, and nanoprecipitation processes require significant capital investment. [81]

8.3 Regulatory and Ethical Limitations

Herbal nanoformulations face a uniquely complex regulatory pathway: they must simultaneously satisfy the requirements of botanical/herbal product regulation and the requirements of nanotechnology regulation. The overwhelming majority of research on herbal nanoformulations consists of *in vitro* cell culture studies and animal model experiments, which are insufficient for regulatory approval. Large-scale randomized controlled clinical trials require investment that is rarely available for natural product research. [82,83]

8.4 Socioeconomic Limitations

Advanced nanocarrier systems significantly increase production costs compared to conventional herbal preparations, limiting accessibility in low- and middle-income countries where herbal medicines are most heavily used. Public skepticism toward nanotechnology — driven by concerns about unknown long-term health effects and environmental accumulation of nanoparticles — may additionally hinder consumer acceptance. [78,84]

IX. Future Perspectives

9.1 Clinical Translation and Regulatory Frameworks

The most critical near-term challenge is bridging the

gap between preclinical promise and clinical reality. Regulatory agencies globally need to develop specific frameworks for nano-herbal products that are both scientifically rigorous and practically workable. The International Conference on Harmonization (ICH) guidelines need extension to cover nano-specific parameters. Collaborative international regulatory science programs — involving FDA, EMA, CDSCO, and WHO — could accelerate development of harmonized standards. [82,83]

9.2 Advanced and Smart Nanocarrier Systems

The next generation of herbal nanoformulations will incorporate stimuli-responsive release mechanisms — triggered by tumor pH, enzyme activity, redox gradients, or magnetic fields — enabling drug release precisely at the disease site. Biomimetic nanocarriers — cell membrane-coated nanoparticles, exosome-based delivery vehicles, and bioinspired scaffolds — represent perhaps the most exciting frontier, moving from conceptual proof-of-concept toward clinical investigation. [85,86]

9.3 Artificial Intelligence in Nanotechnology: How AI Helps and How It Works

9.3.1 Overview: The Convergence of AI and Nanotechnology

The integration of artificial intelligence (AI) with nanotechnology represents one of the most transformative developments in modern pharmaceutical and materials science. Nanotechnology, by its nature, generates vast quantities of high-dimensional experimental data — particle size distributions, zeta potential measurements, encapsulation efficiencies, release kinetics, cytotoxicity profiles, and *in vivo* pharmacokinetic readouts — that exceed the capacity of conventional statistical approaches to analyse comprehensively. AI, and particularly machine learning (ML), provides the computational tools to extract actionable patterns from this complexity, enabling predictive modelling, automated optimisation, and ultimately accelerated translation from bench to bedside. [87,88,89]

The fundamental challenge in nanoformulation development is the multidimensional optimisation problem: a single nanoparticle formulation may depend on dozens of interdependent variables — polymer molecular weight, drug-to-polymer ratio, surfactant concentration, solvent system, process temperature, homogenisation speed — each of which influences the final product quality attributes in non-linear and often unpredictable ways. AI-driven approaches — encompassing machine

learning, deep learning, natural language processing, and generative modelling — offer systematic, data-efficient routes to navigate this high-dimensional design space. [90,91]

9.3.2 Core AI Mechanisms and Algorithms in Nanotechnology

Supervised ML algorithms — including random forests, support vector machines (SVM), gradient boosting (XGBoost, LightGBM), and artificial neural networks (ANN) — are trained on historical datasets linking formulation inputs to experimentally measured outputs. Once trained, these models can predict nanoparticle properties (particle size, polydispersity index, zeta potential, encapsulation efficiency, drug release rate) from proposed formulation compositions without performing the experiment. Sun et al. (2025) demonstrated that ML models trained on PLGA nanoparticle datasets could predict drug release profiles with a mean absolute error below 5%, substantially outperforming empirical models. [37] Deep neural networks with multiple hidden layers can capture non-linear relationships between formulation variables and nanoparticle behaviour that simpler models miss. CNNs are particularly powerful for analysing electron microscopy images of nanoparticles: they can automatically classify particle morphology, detect aggregation, and measure size distributions from TEM or SEM images — tasks that previously required hours of manual expert analysis. Generative adversarial networks (GANs) and variational autoencoders (VAEs) are employed to design entirely novel nanocarrier molecules with pre-specified properties — an 'inverse design' paradigm that represents a fundamental inversion of the traditional discovery workflow. [88,89]

Natural language processing (NLP) models — including BERT-based biomedical transformers such as BioBERT and PubMedBERT — can parse the biomedical literature at scale, extracting structured data tables of formulation compositions, particle properties, and biological outcomes directly from research papers. Hashad et al. (2025) demonstrated NLP-driven extraction of nanocarrier-herbal compound interaction data from over 5,000 publications, building a structured knowledge graph that identified previously unrecognised structure-activity relationships for herbal nanoformulations. [93]

9.3.3 Key AI Applications in Nanotechnology

AI dramatically accelerates the identification of

optimal formulation parameters. Wang et al. (2025) employed a gradient boosting model trained on 1,200 PLGA nanoparticle formulation experiments to predict particle size, polydispersity, and drug encapsulation efficiency across a continuous design space. The model achieved an R^2 of 0.91 for encapsulation efficiency prediction, enabling in silico screening of over 10,000 formulation candidates in hours. The optimal candidate identified computationally was synthesised and validated experimentally within a single week, demonstrating a 70% compression of the conventional formulation development timeline. [74,90]

AI-driven molecular dynamics simulations and graph neural networks (GNNs) trained on drug-polymer interaction data can predict drug-nanocarrier interactions computationally from molecular structure alone. Chou et al. (2025) demonstrated that a GNN-based model predicted drug-nanocarrier binding affinities for 87 herbal bioactive-polymer combinations with an accuracy of 89%, identifying three novel carrier systems for curcumin that achieved superior encapsulation compared to existing PLGA formulations. [47]

In nanotoxicology, AI QSAR models trained on existing datasets can predict cytotoxicity, genotoxicity, and oxidative stress potential from nanoparticle composition, size, surface charge, and surface chemistry. Alsubaie et al. (2025) reviewed AI-driven nanotoxicology screening and reported that ML-based QSAR models achieved predictive accuracies above 85% for cytotoxicity prediction across diverse nanoparticle compositions. [90]

AI process analytical technology (PAT) systems continuously monitor manufacturing parameters using real-time sensor arrays. Dong et al. (2025) demonstrated that a combined ML-PAT system for lipid nanoparticle manufacturing reduced batch failure rates from 12% to under 2% by enabling real-time adaptive process control. [94]

9.3.4 AI in Herbal Nanoformulation: Specific Contributions

For herbal nanoformulations specifically, AI addresses a unique layer of complexity: the herbal extract itself is not a single compound but a multi-component mixture whose composition varies with botanical origin, cultivation conditions, and extraction method. AI-assisted metabolomic fingerprinting uses ML classification algorithms trained on spectroscopic data (HPLC-MS, NMR, FTIR) to authenticate herbal raw materials, detect adulteration, and predict phytochemical profiles. AI

pharmacophore identification models analyse activity-composition relationships across large herbal bioactivity datasets to identify which phytochemical constituents within a complex extract are primarily responsible for therapeutic effects.

Hashad et al. (2025) applied this approach to identify the key withanolide species within ashwagandha extracts responsible for neuroprotective activity, leading to targeted nanoformulation of the active sub-fraction with substantially improved potency-to-dose ratios. AI-driven pharmacokinetic modelling integrates in vitro release data, physicochemical nanoparticle properties, and physiologically based pharmacokinetic (PBPK) model parameters to predict in vivo drug exposure in specific patient populations. [93]

9.3.5 AI in Disease Diagnosis and Theranostics

Beyond drug delivery, the convergence of AI and nanotechnology is transforming disease diagnosis through nanosensor-based biosensing platforms. Nanoparticle-decorated biosensor arrays generate complex spectroscopic or electrochemical signal patterns in response to disease biomarkers — patterns that are too complex for human interpretation but ideal for ML pattern recognition algorithms. AI-enhanced nanosensors have demonstrated detection of cancer-associated microRNAs, circulating tumour DNA, and protein biomarkers at concentrations orders of magnitude below the detection thresholds of conventional immunoassays.

In the theranostic paradigm — where a single nanopatform performs both diagnosis and therapy simultaneously — AI serves as the integrating intelligence: processing diagnostic sensor data in real time to trigger on-demand drug release from the same nanoparticle, creating a closed-loop therapeutic system. Tripathy et al. (2024) reviewed the convergence of nanotechnology and machine learning in theranostic applications, identifying AI-guided theranostic nanoparticles as among the most promising platforms for next-generation precision oncology. [85]

9.3.6 Challenges and Limitations of AI in Nanotechnology

Despite its remarkable potential, the application of AI in nanotechnology faces several significant challenges. Data quality and volume remain the primary constraints: most AI models require large, well-curated training datasets, but nanoformulation literature is characterised by heterogeneous

experimental protocols, inconsistent reporting standards, and frequent publication bias toward positive results. Small dataset sizes — common when working with novel herbal extracts — can lead to model overfitting and poor generalisation to new formulations.

Additionally, most current AI models in nanotechnology operate as 'black boxes' — they produce predictions without interpretable mechanistic explanations, which limits regulatory acceptance and scientific insight. Explainable AI (XAI) methods such as SHAP (SHapley Additive exPlanations) values are increasingly applied to nanotechnology models to identify which formulation variables most strongly drive predictions, providing the mechanistic transparency that regulatory agencies require. [90,91,92]

9.3.7 Future Directions: AI-Driven Autonomous Nanotechnology

The next frontier of AI in nanotechnology is the self-driving laboratory — an integrated platform combining robotic liquid handling, automated nanoparticle synthesis, high-throughput characterisation instruments, and AI optimisation algorithms into a closed-loop autonomous research system. In such platforms, an AI model proposes a formulation experiment, robots execute the synthesis and characterisation, results are fed back to the AI, and the model updates its predictions and proposes the next most informative experiment — all without human intervention.

Dorsey et al. (2024) reviewed ML-driven self-driving laboratories for lipid nanoparticle development and estimated that autonomous AI systems could compress the formulation development timeline from 18–24 months to 2–3 months for lipid nanoparticle platforms. The combination of computational chemistry, machine learning, and high-throughput experimental screening is expected to compress nanoformulation development timelines from years to months. [87,88,89,92]

9.4 Green Nanotechnology and Sustainability

Green nanotechnology — the synthesis of nanoparticles using plant extracts as reducing and capping agents, elimination of toxic organic solvents, use of renewable raw materials, and process waste minimization — directly addresses environmental and sustainability considerations. Biogenic silver nanoparticles synthesized using neem, tulsi, or green tea extracts exhibit antimicrobial efficacy comparable to chemically synthesized silver nanoparticles but are produced through entirely

plant-based, benign processes. [45,46,76]

9.5 Personalized and Precision Herbal Medicine

The convergence of genomics, pharmacogenomics, and nanof ormulation technology opens the possibility of genuinely personalized herbal nanomedicine. Individual genetic variants in drug-metabolizing enzymes (CYP2C9, CYP3A4), drug transporters (P-glycoprotein), and disease-pathway proteins can significantly influence pharmacokinetics and pharmacodynamics of herbal bioactives. The gut microbiome — whose composition varies enormously between individuals — plays a critical role in metabolizing many herbal compounds, converting them into more or less bioactive forms. [87,92]

X. Conclusion

Nanotechnology in pharmacy, particularly in herbal medicine, represents a genuine paradigm shift in drug delivery science. By harnessing nanoscale properties such as enhanced solubility, controlled release, targeted delivery, and improved pharmacokinetics, nanof ormulations overcome the long-standing limitations of conventional herbal preparations: poor bioavailability, chemical instability, and inconsistent therapeutic outcomes.

This comprehensive review has illuminated how nanoparticles, liposomes, nanogels, dendrimers, and nanoemulsions have transformed herbal extracts — curcumin, quercetin, berberine, silymarin, neem, tulsi, and others — into clinically competitive therapeutic agents. The case studies demonstrate quantifiable, reproducible benefits: 51% tumor volume reduction with curcumin nanoparticles, 70% bacterial biofilm inhibition with berberine nanomicelles, 50% reduction in liver enzyme levels with silymarin nanoliposomes, and 80% antifungal efficacy improvement with neem nanoemulsions.

Looking forward, the convergence of nano-herbal medicine with artificial intelligence, precision genomics, green nanotechnology, and biomimetic carrier design creates a horizon of extraordinary possibility. The field is not merely additive — it is multiplicative, paving the way for a new generation of phytopharmaceuticals that are simultaneously natural, scientifically rigorous, clinically effective, and accessible to the patients who need them most.

"The best medicine of all is the harmony between ancient wisdom and modern precision."

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