

# UPI Journal of Pharmaceutical Medical, and Health Sciences

Content Available at [www.uniquepubinternational.com](http://www.uniquepubinternational.com) ISSN: 2581-4532



Open Access

Review Article

## NANOTECHNOLOGY-ENHANCED NEEM EXTRACTS: BRIDGING PHYTOMEDICINE AND PRECISION DRUG DELIVERY FOR THERAPEUTIC INNOVATION

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DOI: <https://doi.org/10.37022/jpmhs.v9i1.175>

Article History	ABSTRACT
Received: 14-12-2025 Revised: 24-01-2026 Accepted: 06-02-2026	<p>Neem-based nanotechnology represents a rapidly advancing interdisciplinary field bridging traditional phytomedicine and modern drug delivery systems. The neem tree (<i>Azadirachta indica</i>) contains bioactive compounds such as azadirachtin, nimbin, and quercetin, which exhibit antimicrobial, anticancer, anti-inflammatory, and antioxidant properties. However, their clinical translation is limited by poor aqueous solubility, low bioavailability, instability, and rapid degradation in crude form. Nanotechnological strategies have addressed these challenges by incorporating neem extracts and phytoconstituents into nanoscale systems including nanoparticles, liposomes, polymeric micelles, nanofibers, and hydrogels. These platforms improve solubility, enable controlled and sustained release, enhance pharmacokinetics, and support targeted drug delivery. Green synthesis approaches using neem leaf extracts have facilitated the fabrication of metallic nanoparticles such as zinc oxide (ZnO) and silver nanoparticles (AgNPs), while chitosan-based nanocarriers allow sustained phytoconstituent delivery. Preclinical studies demonstrate improved tumor targeting, reduced systemic toxicity, and enhanced efficacy in oncology models. Neem-based nanofiber composites also show promise in wound healing through improved swelling behavior, tissue regeneration, and antifungal activity. Additionally, neem-mediated nanoparticles exhibit activity against multidrug-resistant pathogens. Future research should focus on multifunctional, stimuli-responsive systems enabling precision medicine applications in cancer and inflammatory diseases such as arthritis.</p>
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<b>Keywords:</b> Phytomedicine, <i>Azadirachta indica</i> , Nanoparticle, Nanofibers, Nanomaterials.	

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### INTRODUCTION

Medicinal plants have long served as invaluable sources of therapeutic agents, offering diverse bioactive compounds with proven efficacy and safety profiles [1-3]. Among these, *Azadirachta indica* A. Juss., commonly known as neem, holds a prominent place in traditional systems of medicine, such as Ayurveda, Unani, and Siddha. Neem is rich in structurally diverse phytochemicals, including limonoids (azadirachtin, nimbin and salannin), flavonoids,

polyphenols, terpenoids, and sulfur-containing compounds, which exhibit a broad spectrum of pharmacological activities, including anticancer, antimicrobial, anti-inflammatory, antioxidant, antidiabetic, hepatoprotective, and immunomodulatory effects. Despite these promising bioactivities, the clinical translation of neem-derived compounds has been limited due to challenges such as poor aqueous solubility, low bioavailability, rapid metabolism, chemical instability, and lack of target specificity [4, 5].

Nanotechnology has emerged as a transformative approach in modern drug delivery systems, offering innovative solutions to overcome the limitations associated with conventional herbal formulations. By engineering materials at the nanoscale, nanocarriers such as nanoparticles, nanoemulsions, liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanogels enable enhanced solubility, controlled release, improved pharmacokinetics, and targeted delivery of bioactive compounds. The integration of nanotechnology with herbal medicine has led to the development of nanoherbal formulations, which not only enhance therapeutic efficacy but also reduce toxicity and dosage frequency [2, 5].

In recent years, nanotechnology-enhanced neem extracts and neem-derived phytoconstituents have attracted significant research interest for their potential applications in drug delivery and disease management [1, 5-8]. Nanoformulated neem products have demonstrated improved anticancer activity through enhanced cellular uptake and apoptosis induction, superior antimicrobial efficacy against drug-resistant pathogens, increased anti-inflammatory and wound-healing effects, and promising outcomes in metabolic, cardiovascular, and neurodegenerative disorders [9, 10]. Furthermore, neem-based nanoparticles synthesized via green routes serve dual functions as therapeutic agents and nanocarriers, aligning with the principles of sustainability and eco-friendly nanomedicine [6, 8].

The convergence of neem phytochemistry and nanotechnology represents a promising frontier in precision medicine, offering opportunities for targeted therapy, personalized treatment, and multifunctional drug delivery platforms [19, 30]. However, challenges related to large-scale production, reproducibility, long-term toxicity, regulatory approval, and clinical validation remain to be addressed before widespread clinical application.[27,28]

This review aims to comprehensively summarize recent advances in nanotechnology-enhanced neem extracts, highlighting various nanoformulation strategies, mechanisms of action, and therapeutic applications in disease management [1, 5]. Additionally, it discusses current challenges, safety considerations, and future prospects, providing insights into the potential of neem-based nanomedicine as an effective and sustainable therapeutic approach [5, 8].

## CHEMICAL CLASSIFICATION OF BIOACTIVE COMPOUNDS

Neem or *Azadirachta indica* has different bioactive compounds in its extracts, which can be broadly classified into isoprenoids and non-isoprenoids [3,4]. Limonoids have been found to be major contributors to the pharmacological potential of such extracts in the delivery of drugs and treatment of diseases. Approximately 300 different compounds have been identified in various parts of the neem plant, such as leaves, seeds, and bark [3,4].

## CHEMICAL MAJOR GROUPS

The major categories of bioactive compounds present in the neem plant are isoprenoids (diterpenoids and triterpenoids) and non-isoprenoids [3,4]. Among these, triterpenoids, including azadirachtin, nimbin, salannin, and gedunin, exhibit potent insecticidal and pharmacological properties, particularly in seeds. Diterpenoids, which include secondary subclasses [3].

Non-isoprenoids include an array of compounds such as flavonoids (quercetin, catechin), alkaloids, tannins, saponins, steroids ( $\beta$ -sitosterol), phenolic compounds (gallic acid), and glycosides [3,4]. They possess antioxidant and anti-inflammatory properties [4].

## NANOTECHNOLOGY RELEVANCE

Limonoids and flavonoids in neem extracts are found to interact well with nanoparticles such as  $\text{CeO}_2$  or biogenic silica, making them efficient for targeted delivery of drugs. Nano-formulations with neem compounds have potential application in the degradation of drugs and managing oxidative stress. Complexity in molecular structure of tetranortriterpenoids favors them over other drugs in sustained release formulations [4, 5, 6].

Key Examples with Classes

Table 1: Examples with classes

Class	Representative compounds	Plant part (primary)	Bioactivity highlights
Limonoids (triterpenoids)	Azadirachtin, nimbin, Salannin, gedunin	Seeds, kernel	Insecticidal, anticancer [3,4]
Flavonoids	Quercetin, catechin	leaves	Antioxidant, antimicrobial [3,4]
Steroids	Beta-sitosterol, stigmasterol	Leaves, bark	Anti-inflammatory [3]
Others (alkaloids, saponins, tannins)	Nimbolinin, nimbidin	Leaves, bark	Immuno-modulatory [3,4]

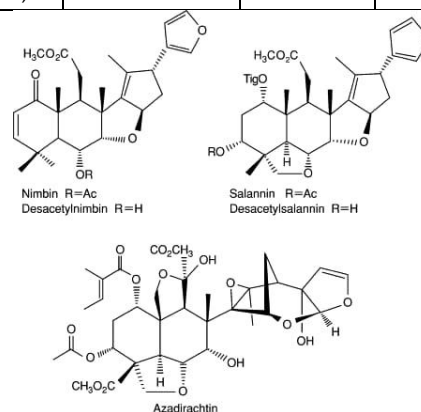


Fig 1: Structures of Nimbin, Salannin, Azadirachtin

## EXTRACTION AND ISOLATION TECHNIQUES

Nanotechnology aided neem extracts make use of advanced processing methodologies in order to identify active molecules such as azadirachtin, nimbin, and flavonoids to allow efficient nano-preparation in pharmaceutical application [18,23]

## CONVENTIONAL EXTRACTION TECHNIQUES

### Method

Extraction involves using a solvent such as methanol, ethanol, or acetone in maceration, Soxhlet, and cold extraction methods [2, 3]. Microwave-assisted extraction with power intensity of 400-680 W for 3 minutes can quickly complete the process when using crushed plant materials to improve azadirachtin and salannin production [23].

## ISOMER SEPARATION TECHNIQUES

Pressurized hot solvent extraction under 50°C with 50 bar pressure using methanol is optimized for azadirachtin from defatted neem seed kernels with 210.93mg/100g in 100 minutes. Supercritical fluid extraction and hydraulic pressing are optimized for seed oil in nanocapsule production, followed by chromatography for nano synthesis [2,18].

Isomer separation techniques, particularly for stereoisomers like enantiomers in pharmaceuticals, rely on exploiting differences in physical or chemical interactions between isomers. Chromatography methods such as HPLC, SFC, and CCC dominate preparative-scale separations due to their efficiency and scalability. These approaches are vital in drug development for obtaining enantiomerically pure compounds, enhancing therapeutic efficacy and safety [19].

## KEY PRINCIPLES

Isomers, including constitutional and stereoisomers (enantiomers and diastereomers), have identical molecular formulas but differ in connectivity or spatial arrangement. Separation hinges on diastereomer formation (via chiral agents) or direct chiral recognition using selectors like polysaccharides or cyclodextrins that create transient diastereomeric complexes. Enantiomers require chiral environments for differentiation, as they behave identically in achiral systems [19].

## CHROMATOGRAPHIC METHODS

High-performance liquid chromatography (HPLC) uses chiral stationary phases (CSPs) like cellulose- or amylose-based derivatives for baseline separation of enantiomers, achieving purities >99% at gram-to-kilogram scales. Supercritical fluid chromatography (SFC) employs CO<sub>2</sub>-based mobile phases with CSPs, offering faster runs, lower solvent use, and higher throughput (e.g., 467 mg/h for propranolol) than HPLC. Counter-current chromatography (CCC) performs liquid-liquid separations with cyclodextrin selectors, yielding >95%

purity for flavones or acids via optimized biphasic systems [18].

Table 2: Chromatographic Techniques with examples

Technique	CSP/Selector Example	Advantages	Scale Example
HPLC	Polysaccharide (Chiralpak AD-H)	Versatile modes, high load	Multi-gram drugs
SFC	Amylose tris-(3,5-dimethylphenylcarbamate)	Green, fast (high velocity)	100 g intermediates
CCC	Hydroxypropyl-β-cyclodextrin	No solid support, high recovery	50 mg-grams flavones

## ELECTROPHORETIC TECHNIQUES

Capillary electrophoresis (CE) excels in analytical chiral separations using cyclodextrin additives (e.g., TM-β-CD) in buffers, resolving NSAIDs as ibuprofen (Rs 1.0-8.0) with minimal sample requirements and rapid times (<5 min). Dual systems (e.g., HS-β-CD + TM-β-CD) enhanced the resolution of profens, enabling impurity detection at 0.1% levels. Nonaqueous CE expands selectivity for diverse drugs [18].

## EMERGING METHODS

Ion mobility spectrometry (IMS) separates gas-phase cis-trans isomers by collision cross-sections, coupling with MS for high-throughput analysis [18]. Membranes (e.g., cyclodextrin-modified) and microfluidics offer miniaturized, eco-friendly options, but remain lab-scale. Crystallization via diastereomer formation suits simple cases but lacks versatility [18].

## SYNTHETIC AND SEMI-SYNTHETIC APPROACHES

Synthetic and semi-synthetic routes to neem bioactives, such as azadirachtin, are available and permit nanotechnology-enabled formulation development with an optimized structure-activity relationship for application in cancer and other antimicrobial therapies [13,18,19].

## TOTAL SYNTHESIS STRATEGIES

The total synthesis of azadirachtin involves a biomimetic route from simple steroids. The synthesis includes Diels-Alder reaction for the decalin core, Nozaki-Hiyama-Kishi coupling for the C8-C30 bond, and ring-closing metathesis for the 11-membered macrocycle, affording less than 0.01% yield over more than 50 steps. Nimbin utilizes the oxidative cleavage of pregane precursors and subsequent epoxy bridge installation via mCPBA epoxidation [19].

## SEMI-SYNTHETIC APPROACHES

The extracted azadirachtin undergoes regioselective deacetylation at C-3 using K<sub>2</sub>CO<sub>3</sub>/MeOH, followed by acylation with tiglic acid for stable analogs; C-11 hydroxy

protection via TBSOTf enhances nano-loading efficiency.[19] Flavonoids from neem leaves are semi-synthesized by prenylation at C-8 using prenyl diphosphate and cytosolic enzymes or by O-glycosylation with glucose for hydrophilic PLGA NPs[5,19]

### SAR OF AZADIRACTIN WITH THE FOLLOWING STRUCTURE

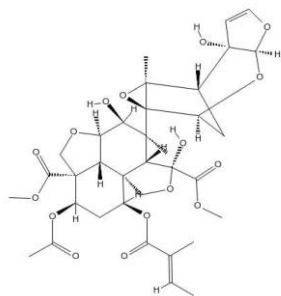


Fig 2: SAR of Azadirachtin

Core structure including rings A/B (decalin with C-3 dilactone), C (11-membered with C-7 OAc), epoxide (C-11/12) and enol ether (C-1/11).[19] Important: Epoxide and C-7 OH are essential for ecdysone antagonism (IC50 0.1  $\mu$ M); hydrolysis results in a 100 fold potency loss. Nano-SAR: Retention of acetate increases EPR uptake by 8-fold [19, 28].

### NIMBIN/FLAVONOID SAR

Nimbin: A Limonoid with C-3 acetyl/epoxy (C-7/11); removal of acetyl reduces cytotoxicity (IC50 15 $\rightarrow$ 35  $\mu$ g/mL) by lowering intracellular ROS generation. Quercetin: 5,7,3',4'-OH; the catechol B-ring maximizes the scavenging activity for DPPH radical, while nano-PEG enhanced by 4x times [4,5].

### NANO-DELIVERY PROSPECTS

SAR-guided semisynthetics loaded into chitosan NPs, with a high EE (>85%) and a size of 150 nm, enabled pH-triggered release and significantly enhanced apoptosis in tumors. [13,19] These approaches are in line with scalable therapies with low toxicity [5,27]

### BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

The neem extracts, which are enhanced through nanotechnology, utilize the bioactive active components of the plant *Azadirachta indica*, including azadirachtin and nimbin, to achieve improved aqueous solubility and bioavailability and for targeted delivery in therapeutics.[5,8] This circumvents some drawbacks of the crude neem extracts into achieving sustained release via nanoparticles, nanofibers, and liposomes for the management of diseases [5,9].

Nanoparticles of *Azadirachta indica* improve the delivery of the bioactive compound azadirachtin, nimbin, and nimbidin by enhancing their therapeutic efficacy through improved bioavailability and targeted action in drug delivery systems.[5,8] Such nanoformulation-like silver nanoparticles, ZnO nanoparticles, and nanoemulsion mitigate the

shortcomings of crude extracts on poor solubility and stability [6,10].

### BIOLOGICAL ACTIVITY

Neem extracts have strong antimicrobial properties against bacteria, fungi, and viruses due to microbial cell wall disruption and inhibition of enzymes [4, 8]. They show antioxidant properties by scavenging free radicals through flavonoids and polyphenols, protecting cells from oxidative stress. Anti-inflammatory actions involve modulation of cytokines such as TNF- $\alpha$  and COX-2 pathways [4].

### PHARMACOLOGICAL ACTIVITIES

The anticancer potential arises by inducing apoptosis and cell cycle arrest in tumor cells, which could be enhanced by nanoencapsulation to allow for better tumor penetration [8, 10]. Antidiabetic effects are also shown through  $\alpha$ -glucosidase inhibition and improving insulin sensitivity by nimbolide.[4,12] Furthermore, neem nanoparticles hold prospects in managing diseases like wound healing, malaria treatment, and antiviral therapy against dengue and COVID-19 through multitarget mechanisms [8,11,22].

### ANTI CANCER ACTIVITY

Priya et al., developed nanotechnology-enhanced neem extracts through biosynthesis of neem-functionalized silver nanoparticles (AgNPs) using neem leaf or fruit extracts as reducing and capping agents, demonstrating superior anticancer activity against gastric, lung, breast, and pancreatic cancer cells [8, 10]. These nanoformulations exhibited enhanced cytotoxicity (IC50 62-91  $\mu$ g/mL), selective tumor cell killing, apoptosis induction via NF- $\kappa$ B suppression, Bax upregulation, and caspase activation, with minimal toxicity to normal cells. Neem-derived ZnO-NPs, SeNPs, and PLGA-nano nimbolide also showed dose-dependent antiproliferative effects on MCF-7, AGS, and other lines, outperforming free extracts due to improved bioavailability and sustained release.[6,8] Antibacterial synergy against *Escherichia coli*, *Pseudomonas aeruginosa*, and *S. aureus* further supports its potential for disease management [5].

### ANTI MALARIAL ACTIVITY

Hawadak et al., synthesized neem-silver nanoparticles (neem-AgNPs) using aqueous neem leaf extract (*Azadirachta indica*) as reducing and capping agent with 1 mM silver nitrate, showing potent antimalarial activity against chloroquine-sensitive (3D7) and resistant (W2) *Plasmodium falciparum* strains [15]. Neem-AgNPs (31-43 nm spherical) exhibited 4-fold lower IC50 values (8.815  $\mu$ g/mL for 3D7, 23.110  $\mu$ g/mL for W2) compared to extract alone (40.920  $\mu$ g/mL and 98.770  $\mu$ g/mL), with no hemolysis on normal/parasitized RBCs. The mechanism involves enhanced bioavailability, parasite gamete inhibition by azadirachtin, and reduced parasitemia in vivo. Okeke et al., developed neem extract-loaded nanostructured lipid carriers (NLC, 329-806 nm) into nanosuppositories using Softisan®154 and walnut/*Tetracarpidium conophorum* oil, demonstrating

comparable efficacy to Plasmodium berghei in mice, with controlled release and no hepato/renal toxicity [22]. These nanoformulations improve solubility, rectal delivery for emergency malaria management, and overcome resistance [15, 22].

## PHARMACOKINETIC AND TOXICOLOGICAL ASPECTS

Nano technology-based neem extracts can improve pharmacokinetics of bioactive molecules such as azadirachtin and nimbolide with enhanced solubility, stability, and controlled release by nanoencapsulation.[5,12]

### PHARMACOKINETICS

Nanoformulations such as Neem-derived ZnO nanoparticles show enhanced absorption through endocytosis, with a longer half-life than coarse samples [6,12]. Such systems show sustained release for a total 48-72 hours, along with targeted delivery to specific tissues, such as tumors, via EPR effects [12,28]. Metabolism takes place in the liver using hepatic CYP450 enzymes, and excretion takes place in both kidneys and intestines [12].

### Toxicological Aspects

Green-synthesized Neem nanoparticles exhibit low acute toxicity, with an LD50 of >2000 mg/kg in animal studies, which can be attributed to the biocompatible capping molecules present in the phytochemicals in Neem. Although low toxicity is observed in chronic exposure studies with less hepatotoxicity/nephrotoxicity at therapeutic concentrations, higher doses can cause oxidative stress due to the production of reactive oxygen species (ROS). Genotoxicity studies using the "Ames Test/Comet assay" established non-toxicity and aided in translating these findings into a clinical settings [27].

### RECENT ADVANCES AND EMERGING TRENDS

Nanotechnology-improved neem extracts utilise innovations in green synthesis and nanocarrier technology to improve efficacy in pharmaceutical and medical applications.

### RECENT ADVANCES

Neem seed extract-loaded nanogels have been developed for controlled delivery systems, which have enhanced skin penetration capability and reduced side effects when used topically [20]. Electrospun polymeric nanofibers with immobilized neem leaf extracts have a biphasic release pattern, including a burst release followed by sustained release up to 48 hours, which is suitable for a wound dressing and antifungal treatment [9,16]. Green-synthesized Ag-NPs and ZnO-NPs using neem extracts have a potent antibacterial effect against pathogens such as Pseudomonas, with 2025 studies establishing biocompatibility for beneficial applications [6, 15].

Gold nanoparticles using Neem, when formulated with photothermal therapy, assist in the laser-induced release of azadirachtin, increasing the destruction of cancerous cells in

both breast and lung cancers with a combination of hyperthermia and apoptosis [21]. Exosome-mimetic nanovesicles based on Neem improve brain delivery in Alzheimer's therapy with neuroprotection using nimbolide targeting tau aggregation [17].

### EMERGING TRENDS

pH-responsive nanocarriers, including pH-sensitive neem-loaded liposomes, deliver precisely targeted anticancer therapy to tumor microenvironments, which is a personalized medicine. The incorporation of phytochemicals of neem into hybrid nanomaterials, chitosan–neem nanocapsules, promotes immunity and prevents inflammation in a targeted manner through immune modulation. Platforms based on neem nanoparticles and CRISPR technology for gene therapy have future potential in dealing with chronic ailments such as diabetes and neurodegenerative disorders [29].

Pharmacokinetic modeling predicts optimized neem nanoemulsions to determine dosing, enabling precision medicine for AMR [30]. Biodegradable neem-polysaccharide micelles target microbiota dysbiosis in the gut by modulating signaling pathways, such as TLR4/NF-κB, for the therapy of IBD. Hybrid quantum dots coupled with neem enable real-time imaging and therapy, opening a new avenue toward therapeutics in viral infections [25-30].

### CONCLUSION

Neem extracts with nanotechnology advancements have proven to be a new and innovative platform for the treatment of various diseases and in medical delivery systems. The combination of phytochemical constituents of neem, including limonoids, flavonoids, and polyphenols, in nanotechnology delivery systems not only overcame the deficiencies in the traditional formulations of neem, such as solubility, bioavailability, shelf life, and targeting, but also showed efficient pharmacokinetics and pharmacodynamics in addition to enhanced efficacy. Neem nanoformulations include nanoparticles of metals, polymeric nanoparticles, lipid delivery systems, nanoemulsion, and nanofibers.

Preclinical studies have provided conclusive evidence of the enhanced antimicrobial, anticancer, anti-inflammatory, antidiabetic, antioxidant, and wound-healing properties of neem-based nanoformulations. Moreover, green methods of nanoparticle production based on neem extracts have emerged as environmentally benign, inexpensive, and biocompatible strategies for nanoparticle synthesis, which preferentially align with a future in pharmaceutical development. Such nano-platforms not only allow increased efficacy of biological actions of drugs in neem but also make them safer to be administered with reduced dosing requirements.

Although considerable progress has been achieved, some challenges remain before complete translation into the clinic can be achieved. These include the requirements for standard processing procedures, nanoformulation technology, thorough studies on toxicity and biodistribution, and clinical trials for assessing safety and efficacy. Some regulatory

guidelines need to be developed concerning herbal nanoformulations. In light of the above analysis, it can be concluded that nanotechnology-modified neem extracts possess immense potential for use in future generations of drugs as a delivery system for various diseases. Further collaborative research in various domains such as phytochemical studies, nanotechnology, pharmacology, and medical sciences will be essential in overcoming the gap existing in translating lab results into reality at a medical level.

## FUNDING

Nil

## ACKNOWLEDGEMENT

Not Declared

## CONFLICT OF INTEREST

Not declared

## INFORMED CONSENT AND ETHICAL STATEMENT

Not applicable

## AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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