International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 7, July 2026 **ijppr.humanjournals.com** ISSN: 2349-7203

Harnessing *Azadirachta indica* for Antifungal Nanomedicine: Beyond Imidazole Synergy

Mr. Nikhil Bapusaheb Magdum, Ms. Saniya P. Savardekar, Dr. Jyoti G. Kadkol

Department of Pharmaceutics, Appasaheb Birnale College of Pharmacy, Sangli 416416. India.

Received: 27 May 2026 Revised: 15 June 2026 Accepted: 28 June 2026

ABSTRACT

Fungal infections are a major global health concern due to their increasing occurrence, recurrence, and development of resistance against existing antifungal therapies. Azole antifungal drugs, especially imidazole derivatives, are commonly used for treatment; however, limitations such as poor solubility, reduced penetration, prolonged therapy, and resistance reduce their effectiveness [1].Nanotechnology has emerged as a promising approach to improve antifungal therapy by enhancing drug delivery, bioavailability, and controlled release of therapeutic agents [2]. Green synthesis of nanoparticles using medicinal plants provides an eco-friendly and biocompatible alternative to conventional synthesis methods [3].*Azadirachta indica* (Neem) contains several bioactive compounds including azadirachtin, nimbin, flavonoids, phenolics, and terpenoids that possess antimicrobial properties and act as reducing and stabilizing agents during nanoparticle synthesis [4]. Neem-mediated nanoparticles such as silver, zinc oxide, and copper oxide nanoparticles exhibit enhanced antifungal activity through reactive oxygen species generation, membrane disruption, inhibition of biofilm formation, and interference with fungal metabolism [5].This review summarizes the role of *Azadirachta indica*-based nanomedicine in antifungal therapy, including phytochemical contribution, green synthesis approaches, mechanisms of action, synergistic potential with imidazole drugs, and future applications in topical antifungal formulations.

Keywords: *Azadirachta indica*, Neem, antifungal nanomedicine, nanoparticles, green synthesis, imidazole drugs, biofilm inhibition, topical delivery.

1. INTRODUCTION

Fungal infections affect millions of people worldwide and range from superficial infections such as dermatophytosis and candidiasis to life-threatening invasive infections [1]. Increasing antifungal resistance has become a significant challenge due to prolonged use of antifungal drugs and limited availability of new therapeutic agents [6].

Azole antifungal agents including clotrimazole, miconazole, and ketoconazole act by inhibiting fungal ergosterol synthesis through inhibition of lanosterol 14α-demethylase. Ergosterol depletion results in altered membrane structure and inhibition of fungal growth [7]. However, resistance mechanisms including enzyme modification and increased drug efflux reduce treatment success [8].

Nanotechnology provides an innovative platform for improving antifungal activity by increasing drug stability, enhancing penetration, and enabling targeted delivery [2]. Plant-mediated nanoparticle synthesis has gained attention due to its simplicity, low cost, and reduced toxicity.

Among medicinal plants, *Azadirachta indica* (Neem) has significant importance because of its broad antimicrobial activity and ability to synthesize biologically active nanoparticles. Neem-derived nanoparticles combine plant phytochemicals with nanoscale properties, providing enhanced antifungal effects.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 7, July 2026 ijppr.humanjournals.com ISSN: 2349-7203

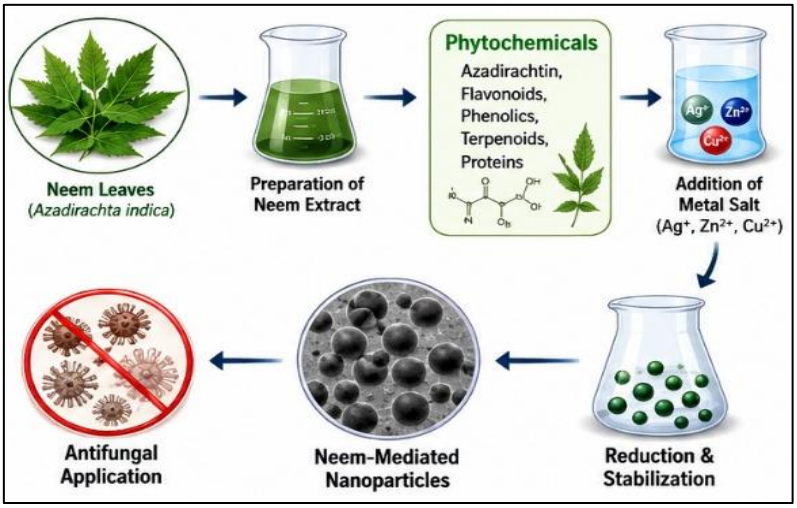


Figure 1.Green synthesis of neem-mediated nanoparticles

2. PHYTOCHEMICAL PROFILE OF *Azadirachta indica*

Neem contains various secondary metabolites responsible for its pharmacological activities. The major phytoconstituents include limonoids, flavonoids, phenolic compounds, and terpenoids [4].

Table 1.Major phytoconstituents of neem and their role

Compound	Activity
Azadirachtin	Antimicrobial activity
Nimbin	Anti-inflammatory and antifungal effect
Nimbidin	Membrane disruption
Flavonoids	Antioxidant and antimicrobial action
Phenolics	Microbial growth inhibition
Terpenoids	Membrane interaction

These phytochemicals donate electrons during nanoparticle synthesis and act as natural capping agents, improving nanoparticle stability [3].

3. GREEN SYNTHESIS OF NEEM-MEDIATED NANOPARTICLES

Green synthesis of nanoparticles has gained significant attention as an alternative approach to conventional physical and chemical methods. Chemical synthesis often involves hazardous reducing agents and stabilizers that may cause environmental and biological concerns. Plant-mediated synthesis provides a safer, economical, and sustainable method by utilizing naturally occurring phytochemicals as reducing and capping agents [3].

In plant-assisted synthesis, metal ions interact with phytoconstituents present in plant extracts. Functional groups such as hydroxyl, carbonyl, and phenolic groups donate electrons and reduce metal ions into nanoparticles. The same phytochemicals stabilize the formed nanoparticles and prevent aggregation, resulting in biologically active nanostructures [4].

Azadirachta indica leaf extract has been extensively explored for nanoparticle synthesis due to the presence of flavonoids, terpenoids, phenolics, and proteins. These compounds enhance nanoparticle formation and contribute additional antimicrobial activity [5].

Neem-mediated nanoparticles possess unique characteristics including small particle size, large surface area, enhanced cellular interaction, and improved biological activity, making them suitable candidates for antifungal applications.

3.1 Neem-Mediated Silver Nanoparticles (AgNPs)

Silver nanoparticles are among the most widely studied antimicrobial nanomaterials. Neem phytochemicals assist in the reduction of silver ions and produce stable silver nanoparticles.

Neem-mediated AgNPs exhibit antifungal activity by:

• Producing reactive oxygen species

• Damaging fungal cell membranes

• Altering intracellular components

• Inhibiting fungal growth and spore formation

Studies have reported enhanced activity of silver nanoparticles against fungal species including *Candida albicans* and dermatophytes [6].

3.2 Neem-Mediated Zinc Oxide Nanoparticles (ZnO-NPs)

Zinc oxide nanoparticles possess strong antimicrobial properties due to their ability to generate oxidative stress and interact with microbial membranes.

Neem-derived ZnO nanoparticles show antifungal effects through:

• ROS generation

• Membrane damage

• Protein dysfunction

• Inhibition of fungal proliferation

Their biocompatibility and stability make them suitable for topical antifungal formulations [7].

3.3 Neem-Mediated Copper Oxide Nanoparticles (CuO-NPs)

Copper oxide nanoparticles demonstrate broad antimicrobial activity due to their interaction with cellular proteins and enzymes.

Neem-mediated CuO nanoparticles enhance antifungal action by:

• Increasing oxidative stress

• Disrupting cellular metabolism

• Affecting fungal membrane integrity

These nanoparticles may provide an alternative approach for managing resistant fungal infections. [8]

Table 2.Nanoparticle and mechanism

Nanoparticle	Antifungal mechanism
Silver nanoparticles	ROS generation, membrane damage
Zinc oxide nanoparticles	Oxidative stress, growth inhibition
Copper oxide nanoparticles	ROS generation, membrane disruption, enzyme inhibition, oxidative stress

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 7, July 2026 ijppr.humanjournals.com ISSN: 2349-7203

4. ANTIFUNGAL MECHANISMS OF NEEM-DERIVED NANOPARTICLES

Neem-based nanoparticles act against fungi through multiple mechanisms, which provides an advantage over conventional single-target antifungal drugs.

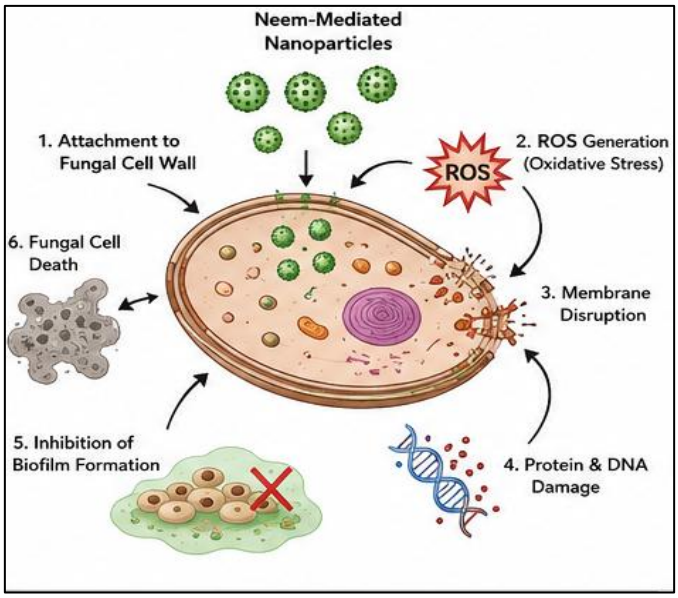


Figure 2 Antifungal Mechanisms of Azadirachta indica-Derived Nanoparticles

4.1 Reactive Oxygen Species Generation

Nanoparticles induce the production of reactive oxygen species (ROS) inside fungal cells. Excess ROS causes oxidative damage to proteins, lipids, and DNA, resulting in loss of cellular function and fungal death [9].

4.2 Disruption of Fungal Cell Membrane

The fungal membrane is essential for maintaining cellular stability. Nanoparticles attach to the fungal surface and disturb membrane integrity, causing leakage of intracellular substances.

This mechanism may improve the effectiveness of azole drugs by increasing fungal membrane permeability.

4.3 Inhibition of Fungal Biofilm Formation

Biofilm formation is one of the major reasons for persistence and recurrence of fungal infections. Fungal biofilms consist of microbial communities surrounded by an extracellular polymeric matrix that protects cells from antifungal agents and immune responses [10].

Neem-mediated nanoparticles interfere with different stages of biofilm development including:

• Initial fungal adhesion

• Hyphal formation

• Biofilm maturation

• Extracellular matrix production

By preventing biofilm formation, neem nanoparticles improve antifungal effectiveness and may help overcome drug-resistant infections.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 7, July 2026 ijppr.humanjournals.com ISSN: 2349-7203

4.4 Inhibition of Fungal Metabolism

Nanoparticles can interact with important cellular molecules including proteins, enzymes, and nucleic acids. This interaction affects essential metabolic pathways required for fungal survival.

Metal oxide nanoparticles may bind with sulfhydryl groups of proteins, resulting in enzyme inactivation and disturbance of normal fungal metabolism [11].

5. SYNERGY BETWEEN NEEM NANOPARTICLES AND IMIDAZOLE ANTIFUNGAL DRUGS

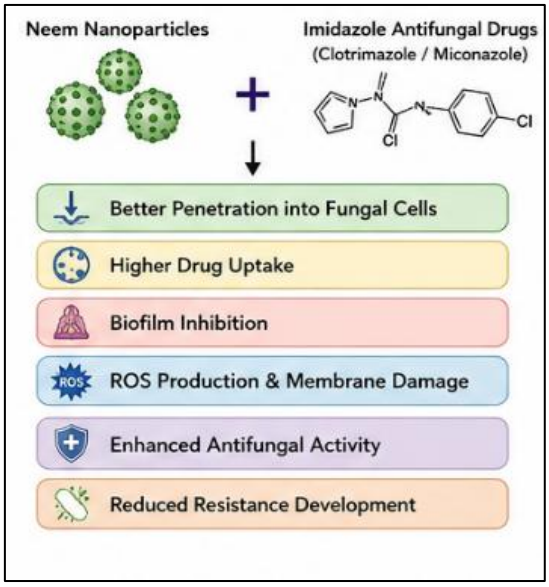


Figure 3 Synergistic Antifungal Action of Neem-Mediated Nanoparticles with Imidazole Antifungal Drugs.

Imidazole antifungal agents such as clotrimazole, miconazole, and ketoconazole are commonly used for topical fungal infections. Their primary mechanism involves inhibition of lanosterol 14α-demethylase, leading to reduced ergosterol production and disruption of fungal membrane function [12].

Table 3.Characterization techniques of neem nanoparticles

Technique	Purpose
UV–Visible Spectroscopy	Nanoparticle formation
FTIR	Functional groups
XRD	Crystal structure
SEM	Surface morphology
TEM	Particle size and shape
DLS	Particle size distribution
Zeta Potential	Stability

Although effective, prolonged use of imidazole drugs may result in reduced sensitivity and resistance due to changes in drug targets, increased efflux pump activity, and adaptive fungal responses [13].

Combination of neem-derived nanoparticles with imidazole drugs provides a multi-target therapeutic approach. Nanoparticles enhance antifungal activity by improving drug delivery and increasing interaction with fungal cells.

Advantages of nanoparticle–azole combinations include:

• Improved drug solubility

• Enhanced penetration into fungal cells

• Controlled drug release

• Reduction in required drug concentration

• Better activity against resistant strains

Table 4.Potential benefits of neem nanoparticle–azole combination

Feature	Effect
Nanoparticle carrier	Improved drug delivery
Neem phytochemicals	Additional antifungal activity
ROS generation	Increased fungal damage
Biofilm inhibition	Reduced recurrence
Controlled release	Longer therapeutic action

6. APPLICATIONS IN TOPICAL ANTIFUNGAL NANOMEDICINE

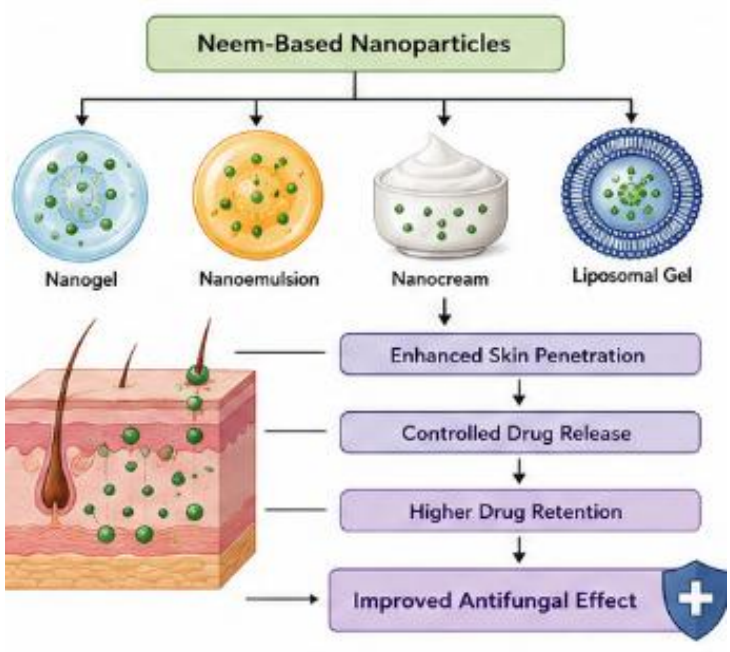


Figure 4.Applications of Neem-Based Nanoparticles in Topical Antifungal Drug Delivery.

Topical antifungal therapy is widely used for treatment of skin infections. However, conventional formulations often show limitations such as poor penetration, rapid removal, and inadequate drug retention.

Neem-based nanocarriers provide improved therapeutic performance due to their nanoscale size and ability to interact with biological barriers.

6.1 Nanogels

Nanogels are three-dimensional nanoscale systems capable of carrying active molecules. They provide controlled release and improve residence time on the skin surface.

Neem-loaded nanogels may enhance antifungal activity by maintaining prolonged contact with infected areas.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 7, July 2026 ijppr.humanjournals.com ISSN: 2349-7203

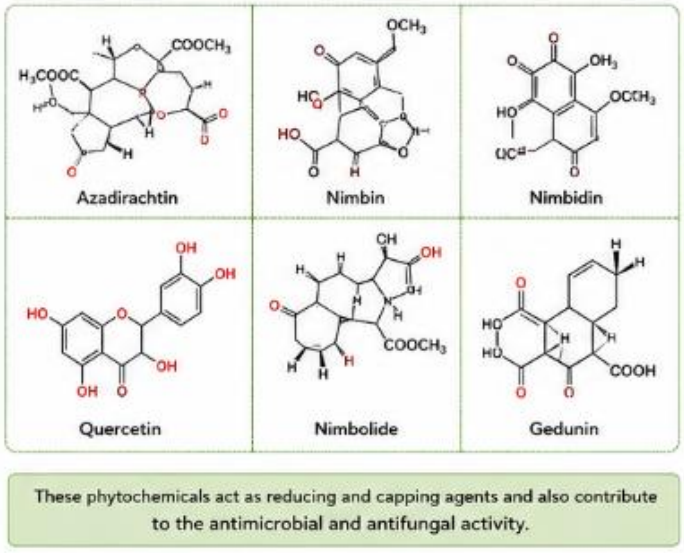


Figure 5.Major Bioactive Phytoconstituents of Azadirachta indica Involved in Nanoparticle Synthesis and Antifungal Activity

6.2 Nanoemulsions

Nanoemulsions improve the solubility of poorly water-soluble antifungal drugs. They enhance drug diffusion through skin layers and improve bioavailability.

3 Nanocreams and Topical Formulations

Incorporation of neem nanoparticles into creams and gels may provide:

• Better skin penetration

• Improved stability

• Reduced irritation

• Prolonged antifungal action

7. CHALLENGES AND FUTURE PERSPECTIVES

Although neem-mediated nanoparticles show promising antifungal potential, several challenges must be considered before their practical clinical application.

The major limitations include:

• Lack of standardization in nanoparticle synthesis methods

• Variation in phytochemical composition of plant extracts

• Difficulty in controlling particle size and morphology

• Limited toxicity and safety data

• Need for large-scale production methods

• Requirement of clinical validation studies

The biological activity of plant-mediated nanoparticles depends on several factors including extraction method, concentration of plant extract, metal precursor, reaction conditions, and nanoparticle characteristics. Therefore, optimization and characterization are essential for reproducible therapeutic outcomes [14].

Future research should focus on developing advanced neem-based nanocarriers with improved targeting ability, controlled release properties, and enhanced safety profiles. Combination therapy involving neem nanoparticles with existing antifungal drugs may provide an effective strategy against resistant fungal pathogens.

The integration of green nanotechnology with traditional medicinal plants may support the development of sustainable antifungal formulations with improved therapeutic performance.

8. CONCLUSION

Azadirachta indica-mediated nanotechnology represents a promising approach for the development of advanced antifungal therapies. Neem phytoconstituents contribute to nanoparticle formation and enhance biological activity through their antimicrobial properties.

Neem-derived nanoparticles such as silver, zinc oxide, and copper oxide nanoparticles exhibit antifungal effects through multiple mechanisms including reactive oxygen species generation, membrane disruption, inhibition of biofilm formation, and interference with fungal metabolism.

The combination of neem-based nanoparticles with imidazole antifungal drugs may overcome limitations associated with conventional therapy by improving drug delivery, penetration, and antifungal effectiveness.

Although further studies are required to establish safety, stability, and clinical efficacy, neem-based antifungal nanomedicine provides a promising and sustainable platform for future therapeutic development.

REFERENCES

1. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases—estimate precision. *J Fungi*. 2017;3(4):57.
2. Cowen LE, Sanglard D, Howard SJ, Rogers PD, Perlin DS. Mechanisms of antifungal drug resistance. *Cold Spring Harb Perspect Med*. 2015;5(7):a019752.
3. Iravani S. Green synthesis of metal nanoparticles using plants. *Green Chem*. 2011;13:2638-2650.
4. Subapriya R, Nagini S. Medicinal properties of neem leaves: a review. *Curr Med Chem Anticancer Agents*. 2005;5(2):149-156.
5. Ahmed S, Ahmad M, Swami BL, Ikram S. A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications. *J Adv Res*. 2016;7(1):17-28.
6. Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. *Biotechnol Adv*. 2009;27(1):76-83.
7. Sirelkhatim A, Mahmud S, Seeni A, Kaus NHM, Ann LC, Bakhori SKM, Hasan H, Mohamad D. Review on zinc oxide nanoparticles: antibacterial activity and toxicity mechanism. *Nano-Micro Lett*. 2015;7:219-242.
8. Lemire JA, Harrison JJ, Turner RJ. Antimicrobial activity of metals: mechanisms, molecular targets and applications. *Nat Rev Microbiol*. 2013;11:371-384.
9. Kim KJ, Sung WS, Moon SK, Choi JS, Kim JG, Lee DG. Antifungal effect of silver nanoparticles on dermatophytes. *J Microbiol Biotechnol*. 2008;18(8):1482-1484.
10. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. *Clin Microbiol Rev*. 2002;15(2):167-193.
11. Lemire JA, Harrison JJ, Turner RJ. Metal nanoparticles and oxidative stress mechanisms. *Nat Rev Microbiol*. 2013;11:371-384.
12. Odds FC, Brown AJP, Gow NAR. Antifungal agents: mechanisms of action. *Trends Microbiol*. 2003;11(6):272-279.
13. Sanglard D. Emerging threats in antifungal-resistant fungal pathogens. *Front Med*. 2016;3:11.
14. Rai M, Ingle AP, Birla S, Yadav A, Santos CA. Strategic role of nanotechnology in fungal infections. *Nanomedicine*. 2015;10(15):2359-2375.
:::

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 7, July 2026 **ijppr.humanjournals.com** ISSN: 2349-7203

How to cite this article:
Mr. Nikhil Bapusaheb Magdum et al. Ijppr.Human, 2026; Vol. 32 (7): 499-507.

Conflict of Interest Statement: All authors have nothing else to disclose.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.