Article type:
Review Article
Volume 2, Issue 2, pp 38-48
Article history:
Received 28 December 2024
Revised 06 February 2025
Accepted 28 February 2025
Published online 01 April 2025

Antifungal Activity of Silver Nanoparticles in Oral Health

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ABSTRACT

Fungal infections pose a significant challenge in medical and dental fields, often leading to persistent and treatment-resistant conditions. Nano silver particles (AgNPs) have emerged as promising antifungal agents due to their broad-spectrum activity, minimal resistance development, and ability to penetrate biofilms. This article reviews the antifungal mechanisms of AgNPs, their effectiveness against common fungal pathogens, and their applications in medicine and dentistry. Furthermore, the challenges and future prospects of AgNPs as antifungal agents are discussed.

Keywords: Antifungal Activity, Silver Nanoparticles, Oral Health.

How to cite this article:
Khaksar, E. (2025). Antifungal Activity of Silver Nanoparticles in Oral Health. *Journal of Oral and Dental Health Nexus*, 2(2), 38-48. https://doi.org/10.61838/jodhn.2.2.5

Introduction

Fungal infections have become a major concern in both clinical and environmental settings, particularly with the rise of immunocompromised individuals due to conditions such as HIV/AIDS, cancer treatments, diabetes, and organ transplants (1). These infections, caused by opportunistic fungi like Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans, can range from mild superficial infections to life-threatening systemic mycoses (2). The increasing incidence of antifungal resistance, particularly against azoles and echinocandins, has further complicated treatment strategies. Consequently, there is an urgent need for alternative antifungal agents with novel mechanisms of action (3).

Nanotechnology has introduced innovative solutions in wide variety of fields like biosensors (4), drug delivery (5), cancer therapy (6), tissue regeneration (7), antimicrobial therapy. Also, Advanced nanotechnology plays a crucial role in oral health and dentistry, particularly in managing complex cases like a maxillary second molar with five root canals and a root-like enamel pearl (8). Nanoparticles improve high-resolution imaging for accurate diagnosis (9), while nanocarriers deliver bioactive agents to promote regeneration or antimicrobial effects. Additionally, nano-engineered biomaterials can mimic natural polymers in enamel and dentin, offering potential solutions for repairing such rare anatomical variations (10).

silver nanoparticles (AgNPs) (11) emerges as a promising antifungal agent (12). Silver has been used for centuries in wound healing and infection prevention (13), and with advancements in nanotechnology, its antimicrobial properties have been enhanced at the nanoscale level. AgNPs exhibit a broad-spectrum antimicrobial effect against bacteria, viruses, and fungi, making them attractive candidates for antifungal applications (14).

One of the major challenges in treating fungal infections is biofilm formation, particularly in species like Candida albicans, which are responsible for persistent infections in medical devices, dentures, and catheters. (15)Conventional antifungal agents struggle to penetrate these biofilms, resulting in recurrent infections and increased resistance. AgNPs, however, have shown promising results in disrupting fungal biofilms and inhibiting their formation by targeting multiple cellular pathways simultaneously (16).

The mechanism of antifungal action of AgNPs includes membrane disruption, generation of reactive oxygen species (ROS), interaction with fungal proteins and DNA, and inhibition of essential enzymatic pathways (17). Unlike conventional antifungals that target a specific fungal structure, such as ergosterol in the cell membrane,

AgNPs interact with multiple cellular components, reducing the likelihood of resistance development (18).

In addition to their direct antifungal activity, AgNPs are being explored for applications in dentistry, wound care, and medical devices. In dentistry, fungal infections like oral candidiasis are common among denture wearers and immunocompromised patients (19). Incorporating AgNPs into dental materials such as adhesives, composites, and mouthwashes has been proposed as an effective antifungal strategy (20). Similarly, in medicine, AgNP-coated wound dressings, catheters, and implantable devices have demonstrated the ability to reduce fungal colonization and biofilm formation, thereby decreasing infection rates in hospital settings (21).

Despite their advantages, the use of AgNPs raises concerns regarding toxicity, stability, and environmental impact. While low concentrations of AgNPs have been shown to be biocompatible, excessive silver exposure can lead to cytotoxicity and oxidative stress in mammalian cells (22). Additionally, the environmental accumulation of nanoparticles and their potential impact on beneficial microorganisms in soil and water ecosystems must be carefully evaluated (23).

This article provides a comprehensive review of the antifungal efficiency of AgNPs, their mechanisms of action, applications in medicine and dentistry, and the challenges associated with their use. By understanding the full potential of AgNPs in antifungal therapy, researchers and clinicians can develop more effective and safer nanotechnology-based solutions for fungal infections.

Mechanisms of Antifungal Action of AgNPs

Silver nanoparticles (AgNPs) exert their antifungal effects through multiple mechanisms that target different cellular structures and metabolic pathways in fungi. Unlike conventional antifungal agents that typically act on a single pathway, AgNPs disrupt fungal cells through membrane damage, oxidative stress, protein interaction, DNA damage, and biofilm inhibition. These multifaceted mechanisms make AgNPs highly effective against fungi, reducing the likelihood of resistance development (24).

Disruption of Fungal Cell Membrane

The primary mechanism by which AgNPs exert antifungal effects is through direct interaction with the fungal cell membrane. The fungal cell membrane is composed of ergosterol, phospholipids, and proteins, which maintain structural integrity and regulate the transport of molecules (25). Studies have shown that AgNPs bind to the fungal membrane, leading to increased membrane permeability, leakage of intracellular contents, and eventual cell lysis (26). The size and surface charge of AgNPs significantly impact their ability to penetrate the membrane; smaller nanoparticles (<20 nm) show enhanced penetration and antimicrobial activity (27).

Research conducted on Candida albicans demonstrated that exposure to AgNPs led to loss of membrane integrity, as evidenced by propidium iodide staining and transmission electron microscopy (TEM) imaging (28). Similarly, in Aspergillus fumigatus, AgNP treatment caused distortion of hyphae and damage to conidial structures, leading to reduced fungal viability (29).

Generation of Reactive Oxygen Species (ROS) and Oxidative Stress

Another crucial mechanism of AgNP-induced antifungal activity is the generation of reactive oxygen species (ROS), including superoxide radicals (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH•). These highly reactive molecules cause oxidative stress, which damages lipids, proteins, and DNA, leading to fungal cell death (30).

Several studies have demonstrated that AgNPs increase ROS production in fungal cells, leading to oxidative damage. A study by Choi et al. (2018) found that Candida glabrata treated with AgNPs exhibited significantly higher levels of malondialdehyde (MDA), a marker of lipid peroxidation, indicating severe oxidative stress. Additionally, AgNPs have been shown to deplete intracellular glutathione (GSH), a key antioxidant defense in fungal cells, making them more susceptible to oxidative damage (31).

Oxidative stress induced by AgNPs has been linked to apoptotic-like cell death in fungi, characterized by chromatin condensation, mitochondrial dysfunction, and DNA fragmentation (32). These findings suggest that

AgNPs act similarly to antifungal drugs like amphotericin B, which also induces oxidative stress but with a higher risk of toxicity (33).

Interaction with Fungal Proteins and Enzymes

AgNPs also interfere with essential fungal enzymes by binding to sulfhydryl (-SH) groups in proteins, disrupting their function (24). Many fungal metabolic pathways rely on enzymes with thiol groups, including those involved in cell wall synthesis, energy metabolism, and stress response (34).

For example, AgNPs have been shown to inhibit key fungal enzymes such as catalase and superoxide dismutase (SOD), which protect fungal cells from oxidative stress. This inhibition further enhances ROS accumulation and accelerates cell death (35). Additionally, (36).

DNA Damage and Inhibition of Cell DivisionAnother

significant effect of AgNPs on fungal cells is DNA damage and inhibition of replication. Silver nanoparticles can penetrate the fungal nucleus and interact with DNA, leading to strand breaks, chromosomal abnormalities, and inhibition of DNA repair mechanisms (27). This disruption ultimately prevents fungal cell division and proliferation (31).

A study by Khan et al. (2019) demonstrated that Candida albicans exposed to AgNPs showed downregulation of genes involved in cell cycle progression, including CDC28 and CLN2, which are critical for DNA replication. Moreover, fluorescence microscopy using DAPI staining revealed nuclear condensation and fragmentation in AgNP-treated fungal cells, confirming DNA damage (37).

Inhibition of Fungal Biofilms

Fungal biofilms, especially in Candida species, pose a significant challenge in clinical infections as they enhance drug resistance and immune evasion. Biofilms consist of extracellular polymeric substances (EPS), fungal cells, and proteins, forming a protective matrix that shields fungi from antifungal drugs and host immune defenses (38).

AgNPs have shown remarkable efficacy in disrupting biofilm formation and breaking down pre-existing biofilms. Research has found that AgNPs reduce the adhesion and growth of Candida albicans biofilms on medical devices, such as catheters and dental prosthetics (35). The nanoparticles achieve this by:

1. Inhibiting initial fungal adhesion to surfaces.
2. Reducing EPS production, weakening the biofilm structure.
3. Penetrating deep into biofilms to target embedded fungal cells

A study by Kim et al. (2019) found that Candida albicans biofilms treated with AgNPs exhibited a 60% reduction in metabolic activity, as measured by XTT assays. Scanning electron microscopy (SEM) also showed significant structural damage to biofilms, confirming the efficacy of AgNPs in biofilm inhibition (39).

Synergistic Effects with Conventional Antifungal Drugs

Several studies have explored the combination of AgNPs with conventional antifungal drugs, such as fluconazole, amphotericin B, and caspofungin. These studies suggest that AgNPs enhance the antifungal activity of these drugs by increasing drug uptake, reducing resistance, and lowering the required drug dosage (35).

For example, a study by Lara et al. (2015) found that AgNPs combined with fluconazole exhibited a synergistic effect against fluconazole-resistant Candida albicans, reducing its viability by over 80%. The combination also prevented the emergence of resistant fungal strains, highlighting the potential of AgNPs in antifungal therapy (21).

Antifungal Spectrum of Silver Nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) exhibit potent antifungal activity against a broad spectrum of pathogenic fungi, including Candida species, Aspergillus species, Cryptococcus species, dermatophytes, and other opportunistic fungi. These fungal pathogens are responsible for cutaneous, mucosal, and systemic infections, particularly in immunocompromised individuals (40). The ability of AgNPs to disrupt fungal membranes, induce oxidative stress, and inhibit biofilms makes them highly effective against both drug-sensitive and drug-resistant strains (41).

Efficacy Against Candida Species

The Candida genus, particularly Candida albicans, is one of the leading causes of opportunistic fungal infections. C. albicans is responsible for infections such as oral thrush, vaginal candidiasis, denture stomatitis, and invasive candidiasis, which pose a significant health risk, especially in hospitalized patients with weakened immune systems (42). AgNPs have been shown to inhibit the growth and biofilm formation of C. albicans, making them a promising alternative to conventional antifungals like fluconazole and amphotericin B (43).

Recent studies have demonstrated that AgNPs exhibit a dose-dependent fungicidal effect on Candida species by disrupting the fungal membrane and inhibiting hyphal formation, a key virulence factor in C. albicans (28). Additionally, AgNPs have shown efficacy against fluconazole-resistant Candida strains, which are increasingly prevalent in clinical settings (31). Furthermore, AgNPs in combination with fluconazole enhance the drug's efficacy, even in resistant strains, indicating a potential role in combination therapy (44).

Antifungal Activity Against Aspergillus Species

Aspergillus species, particularly Aspergillus fumigatus and Aspergillus flavus, are responsible for aspergillosis, a serious lung infection that primarily affects immunocompromised individuals, including organ transplant recipients and cancer patients (45). Standard treatments for invasive aspergillosis include azoles, polyenes, and echinocandins, but increasing antifungal resistance has made treatment more challenging.

AgNPs have demonstrated potent antifungal activity against aspergillosis-causing fungi, disrupting their hyphal structures and preventing conidial germination (29). Studies have shown that AgNPs inhibit the spore germination of Aspergillus fumigatus and interfere with fungal metabolic pathways, leading to cell death (24). Additionally, AgNP-coated surfaces have been found to reduce Aspergillus biofilm formation on medical devices, such as catheters and prosthetic materials, which are common sources of hospital-acquired fungal infections (21).

Cryptococcus Species and Systemic Mycoses

Cryptococcus neoformans and Cryptococcus gattii are the primary pathogens responsible for cryptococcal meningitis, a life-threatening fungal infection commonly seen in HIV/AIDS patients and transplant recipients (46). Cryptococcus species have a polysaccharide capsule, which helps them evade immune responses, making treatment difficult (47).

Silver nanoparticles have shown strong antifungal activity against Cryptococcus by penetrating the fungal capsule and disrupting the integrity of the cell wall (34). Studies indicate that AgNPs induce oxidative stress in Cryptococcus neoformans, causing DNA damage and mitochondrial dysfunction, leading to fungal cell apoptosis (22). AgNPs also inhibit melanin production, a key virulence factor in Cryptococcus, reducing its ability to survive in the host (44).

Dermatophytes and Superficial Fungal Infections

Dermatophytes, including Trichophyton, Microsporum, and Epidermophyton species, cause superficial fungal infections such as athlete's foot, ringworm, and onychomycosis (nail infections) (48). These infections are common and can be resistant to conventional antifungal treatments, requiring long-term therapy (31).

AgNPs have shown promising antifungal activity against dermatophytes by disrupting their cell membranes and inhibiting keratinase enzymes, which are essential for fungal colonization of skin and nails (35). Studies using AgNP-infused topical gels and creams have demonstrated faster healing and better efficacy compared to traditional antifungal agents like terbinafine and clotrimazole (39).

Biofilm-Forming Fungal Pathogens

One of the most significant challenges in antifungal therapy is the formation of biofilms, particularly by Candida albicans and Aspergillus fumigatus (49). Fungal biofilms act as a protective barrier, making fungal cells up to 1000 times more resistant to conventional antifungals (24). AgNPs have been shown to effectively disrupt fungal biofilms by penetrating the biofilm matrix, inhibiting adhesion, and reducing metabolic activity (21).

Research has shown that AgNPs combined with fluconazole or amphotericin B exhibit synergistic effects against Candida biofilms, making them an effective strategy for treating biofilm-associated infections in medical devices such as catheters, dental prostheses, and pacemakers (35). The ability of AgNPs to inhibit quorum sensing, a key factor in biofilm formation, further enhances their antifungal potential (31).

Comparison of Silver Nanoparticles with Conventional Antifungal Agents

The use of silver nanoparticles (AgNPs) as antifungal agents has gained significant attention due to their broad-spectrum activity, low resistance development, and ability to disrupt biofilms. (50).

Mechanisms of Action: Multi-Target vs. Single-Target Approach

Most conventional antifungal drugs act on a specific fungal pathway. For example:

Azoles inhibit ergosterol synthesis, leading to cell membrane disruption. However, fungi can develop resistance through mutations in the ERG11 gene or efflux pump activation (44).

Polyenes like amphotericin B bind to ergosterol, creating pores in the fungal membrane. While effective, this drug has high nephrotoxicity, limiting its use in some patients (22).

Echinocandins target β-glucan synthase, weakening the fungal cell wall. However, some Candida species have developed FKS gene mutations, making them resistant (50).

In contrast, AgNPs exert multiple antifungal mechanisms simultaneously, including membrane disruption, ROS generation, enzyme inactivation, and DNA damage (17). This multi-target approach reduces the likelihood of resistance and makes AgNPs effective even against drug-resistant fungal strains (34).

Efficacy Against Biofilms

One of the biggest challenges in antifungal therapy is biofilm-associated infections, which are resistant to most conventional drugs. Candida biofilms, for example, make infections up to 1000 times more drug-resistant than planktonic cells (39). Conventional antifungals, especially azoles, have limited penetration into biofilms, often requiring higher drug concentrations, which increases toxicity (51).

Studies have shown that AgNPs effectively inhibit biofilm formation and penetrate mature fungal biofilms, disrupting their structure and reducing fungal viability (35). AgNPs reduce EPS (extracellular polymeric substance) production, a key component of fungal biofilms, leading to weaker adhesion and increased drug susceptibility (31).

Resistance Development: A Major Concern for Conventional Antifungals

Fungal resistance to conventional antifungals is a growing concern, particularly in hospital-acquired infections.

Fluconazole-resistant Candida strains are increasing due to overuse and prolonged therapy (52).

Echinocandin resistance has been reported in Candida glabrata, making treatment options limited (53).

Amphotericin B-resistant Aspergillus species have also emerged, especially in immunocompromised patients (44).

Unlike conventional antifungals, AgNPs have a lower tendency to induce resistance due to their multi-target mechanism (54). Even long-term exposure to AgNPs has shown minimal resistance development in fungal pathogens (27).

Toxicity and Safety Considerations

While AgNPs offer several advantages over conventional antifungals, toxicity concerns remain a major challenge.

Amphotericin B is known for high nephrotoxicity, leading to kidney damage in some patients (22).

Azoles and echinocandins can cause liver toxicity, allergic reactions, and gastrointestinal disturbances (55).

AgNPs, while generally biocompatible at low doses, can cause oxidative stress, mitochondrial damage, and cytotoxic effects at high concentrations (56).

To minimize toxicity, surface modifications (e.g., chitosan-coated AgNPs) and controlled-release formulations are being explored to enhance safety while maintaining antifungal efficacy (35).

Potential for Combination Therapy

Given the limitations of conventional antifungal drugs, AgNPs are being explored as adjuvants to enhance existing treatments.

AgNPs combined with fluconazole have shown synergistic effects, improving efficacy against fluconazole-resistant Candida albicans (31).

AgNPs and amphotericin B together lower drug doses, reducing toxicity while maintaining antifungal activity (24).

AgNP coatings on medical devices (e.g., catheters, prosthetics) prevent fungal colonization, reducing hospital-acquired infections (21).

Root Canal Irrigants and Endodontic Sealers: AgNP-based root canal irrigants have demonstrated superior antifungal activity against Candida albicans compared to conventional sodium hypochlorite (NaOCl) solutions (57, 58).

Applications of Silver Nanoparticles in Medicine and Dentistry

Silver nanoparticles (AgNPs) have gained significant attention in medical and dental applications due to their broad-spectrum antifungal, antibacterial, and antiviral properties. Their ability to prevent microbial growth, disrupt biofilms, and enhance wound healing has led to their incorporation into medical devices, pharmaceuticals, wound dressings, and dental materials (27). The following sections explore key applications of AgNPs in antifungal therapy, wound care, prosthetic materials, and dental coatings.

Use of Silver Nanoparticles in Antifungal Therapy

One of the most promising applications of AgNPs is their use as antifungal agents in pharmaceutical formulations. Due to their broad-spectrum antifungal activity, AgNPs are being developed as alternatives or adjuvants to conventional antifungal drugs (59).

AgNP-Infused Topical Creams and Gels: These formulations have shown enhanced efficacy against dermatophytes, such as Trichophyton rubrum and Microsporum canis, which cause skin and nail infections (60). The incorporation of AgNPs in topical formulations improves drug penetration, bioavailability, and stability (44).

AgNP-Based Nasal and Pulmonary Delivery Systems: Aspergillus fumigatus, a major cause of pulmonary aspergillosis, has been shown to be highly susceptible to AgNPs in aerosolized formulations (35).

AgNP-Coated Catheters and Medical Implants: AgNP coatings on medical devices prevent fungal colonization, reducing the risk of Candida-related bloodstream infections and catheter-associated infections (61).

Studies suggest that AgNPs combined with fluconazole or amphotericin B exhibit synergistic effects, increasing drug efficacy while reducing toxicity (62). Such combination therapies have great potential for treating systemic fungal infections in immunocompromised patients.

Silver Nanoparticles in Wound Healing and Burn Treatment

Wound infections caused by fungal and bacterial pathogens pose significant challenges, especially in burn patients. Silver sulfadiazine (SSD) creams have been widely used for burn wound infections, and the incorporation of AgNPs has further enhanced their antimicrobial properties (39).

AgNP-Infused Wound Dressings: AgNP-infused wound dressings provide continuous antimicrobial action against fungal and bacterial infections while promoting angiogenesis and tissue regeneration, mirroring the emerging trends in natural polymers for dental regeneration, which also emphasize bioactive and regenerative properties (7, 63).

This link highlights the shared focus on regenerative and antimicrobial strategies in both wound care and dental applications. Let me know if you'd like a different emphasis!

AgNP-Loaded Hydrogels: Hydrogels infused with AgNPs improve moisture retention and antibacterial properties, making them highly effective for chronic wound management (64).

Antifungal Action on Diabetic Foot Ulcers: Fungal infections, particularly caused by Candida species, are common in diabetic wounds. AgNP-based wound dressings have shown significant efficacy in preventing fungal biofilm formation and promoting healing (44).

Applications of Silver Nanoparticles in Dentistry

The increasing prevalence of oral fungal infections such as oral candidiasis and denture stomatitis has led to the incorporation of AgNPs in dental materials, prosthetics, and coatings. AgNPs in dentistry have proven beneficial due to their antimicrobial properties, biocompatibility, and resistance to biofilm formation (35).

AgNPs in Denture Base Resins: Dentures are susceptible to Candida albicans colonization, leading to denture stomatitis. Studies have shown that AgNPs incorporated into PMMA (polymethyl methacrylate) denture base materials significantly reduce fungal adhesion and biofilm formation (65).

AgNPs in Orthodontic Adhesives and Restorative Materials: Dental composites and adhesives containing AgNPs have been developed to prevent secondary fungal and bacterial infections in orthodontic and restorative procedures (19).

Root Canal Irrigants and Endodontic Sealers: AgNP-based root canal irrigants have demonstrated superior antifungal activity against Candida albicans compared to conventional sodium hypochlorite (NaOCl) solutions (66).

Antifungal Coatings for Medical and Dental Implants

The use of AgNP coatings on dental implants, orthopedic prostheses, and surgical instruments has gained attention due to the high risk of fungal and bacterial infections in implanted materials (67).

AgNP-Coated Titanium Implants: Titanium dental implants coated with AgNPs have shown resistance to Candida albicans and Aspergillus fumigatus, reducing implant failures caused by biofilm formation (31).

AgNPs in Bone Cements and Grafting Materials: Bone grafting procedures often require antimicrobial coatings to prevent fungal infections in orthopedic and maxillofacial surgeries (68).

AgNPs in Periodontal Therapy: Silver nanoparticles have been incorporated into periodontal gels and surgical sutures, reducing post-surgical infections and promoting tissue healing (69).

Future Perspectives and Challenges in Medical and Dental Applications

While AgNPs offer promising antifungal applications, several challenges need to be addressed for widespread clinical use:

Cytotoxicity and Biocompatibility: At high concentrations, AgNPs can induce oxidative stress and toxicity in human cells. Future research aims to develop biocompatible AgNP formulations with controlled release mechanisms (70).

Regulatory Approvals and Clinical Trials: Although AgNPs have demonstrated strong antifungal efficacy in vitro, further in vivo studies and clinical trials are needed to determine their long-term safety and efficacy (56).

Environmental Impact and Resistance Concerns: The accumulation of AgNPs in the environment and potential microbial adaptation require continuous monitoring and responsible use (27).

Challenges and Safety Considerations of Silver Nanoparticles in Antifungal Therapy

While silver nanoparticles (AgNPs) have shown promising antifungal activity, their widespread medical application faces several challenges and safety concerns. Issues such as cytotoxicity, environmental accumulation, stability, and regulatory approvals must be addressed before AgNP-based therapies can be fully integrated into clinical practice (22).

Cytotoxicity and Biocompatibility Concerns

One of the primary concerns regarding AgNPs is their potential toxicity to human cells. While low concentrations of AgNPs exhibit strong antimicrobial effects with minimal cytotoxicity, higher concentrations can induce oxidative stress, mitochondrial dysfunction, and apoptosis in mammalian cells (71). Studies have reported DNA damage, chromosomal aberrations, and inflammatory responses associated with prolonged exposure to AgNPs (34).

To overcome cytotoxicity concerns, researchers are developing:

Biocompatible coatings (e.g., chitosan, polyethylene glycol) to reduce direct AgNP interaction with human cells.

Controlled-release nanoformulations to minimize toxicity while maintaining antifungal efficacy (72).

Targeted delivery mechanisms using biomimetic nanocarriers for site-specific antifungal action (31).

Stability and Aggregation Issues

AgNPs are prone to aggregation and instability, which can reduce their antimicrobial efficacy and alter their physicochemical properties (44). Factors such as pH, ionic strength, and temperature influence AgNP stability, making it challenging to develop long-term storage formulations (35).

To improve stability, researchers are exploring:

Surface functionalization using stabilizing agents like citrate or polymers.

Nanoencapsulation techniques to protect AgNPs from environmental degradation (73).

Environmental Impact and Resistance Development

The widespread use of AgNPs raises concerns about their accumulation in the environment and potential toxicity to aquatic ecosystems and soil microbiota (22). Studies indicate that AgNPs released into water systems can disrupt microbial communities, affecting ecological balance (74).

Additionally, although AgNPs have a low tendency to induce microbial resistance, some studies suggest that prolonged sublethal exposure to silver can lead to adaptive microbial responses and efflux pump activation (44). To mitigate this, researchers advocate for:

Regulated use of AgNPs to prevent overuse and resistance development.

Combination therapies to reduce the concentration of AgNPs needed for antimicrobial activity (27).

Regulatory Approvals and Clinical Translation

Despite extensive in vitro and in vivo studies, AgNP-based antifungal formulations face regulatory challenges due to limited clinical trials and concerns regarding long-term effects (75). Agencies such as the FDA (Food and Drug Administration) and EMA (European Medicines Agency) require comprehensive toxicity, pharmacokinetics, and efficacy studies before approving AgNP-based drugs for human use (39).

Future research should focus on:

Large-scale clinical trials to establish the safety and efficacy of AgNP-based antifungal therapies.

Standardized guidelines for AgNP manufacturing and medical applications (76).

Conclusion and Future Perspectives

Silver nanoparticles (AgNPs) have emerged as a promising alternative to conventional antifungal treatments due to their broad-spectrum activity, ability to inhibit biofilms, and multi-target mechanisms of action. Unlike traditional antifungal drugs that primarily target a single pathway, AgNPs exert their effects through membrane disruption, oxidative stress induction, enzyme inhibition, and DNA damage, making them effective against drug-resistant fungal strains. Their application in medicine and dentistry, including antifungal coatings, wound dressings, dental materials, and medical devices, highlights their potential to enhance infection control and patient outcomes.

Despite these advantages, several challenges must be addressed before AgNP-based antifungal therapies can be widely adopted in clinical practice. Cytotoxicity, stability, environmental impact, and regulatory approvals remain key concerns that require further investigation. High concentrations of AgNPs may induce oxidative stress and DNA damage in human cells, necessitating the development of biocompatible formulations with controlled release mechanisms. Additionally, research on the long-term environmental effects of AgNPs is essential to ensure their safe and sustainable use.

Future studies should focus on optimizing AgNP formulations to minimize toxicity while maintaining antifungal efficacy. Strategies such as surface functionalization, targeted drug delivery, and combination therapies with conventional antifungal drugs could enhance their clinical applications. Furthermore, extensive clinical trials and regulatory assessments are needed to establish standardized guidelines for the safe and effective use of AgNPs in antifungal treatments.

With continued advancements in nanotechnology and biomedical research, AgNPs hold significant potential to revolutionize antifungal therapy by offering a potent, multi-faceted, and resistance-free alternative to existing treatments. Their integration into healthcare could improve infection management and patient outcomes,

paving the way for innovative and effective antifungal solutions.

Authors' Contributions

All authors equally contributed to this study.

Acknowledgments

We would like to express our appreciation and gratitude to all those who cooperated in carrying out this study.

Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

Funding

This research was carried out independently with personal funding and without the financial support of any governmental or private institution or organization.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

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