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REVIEW

Comparison of Metal Nanoparticles as Antifungal Agents: Efficacy, Mechanisms, and Toxicity against *Candida, Aspergillus, and Cryptococcus*

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ABSTRACT

Candida albicans, *Aspergillus fumigatus*, and *Cryptococcus neoformans* are the invasive fungi whose diseases are becoming a growing health issue in the global community, particularly in immunocompromised people. The increasing resistance of the conventional antifungals and the shortage of the existing treatment methods require alternative methods. The present review is an evaluation of the antifungal activity of metal-based nanoparticles, including silver (Ag), copper (Cu), zinc oxide (ZnO), titanium dioxide (TiO_2), and selenium (Se) in relation to the three predominant pathogenic fungi. It also talks about their mode of action, relative efficacy, toxicity and their possible future clinical use. Multimodal effects of metal nanoparticles are reactive oxygen species (ROS) formation, membrane destabilization, and enzyme inhibition, and biofilm disruption. Silver and zinc oxide nanoparticles are very effective against *C. albicans* particularly in biofilm-associated infections. Copper and titanium dioxide nanoparticles also work against *A. fumigatus* and selenium nanoparticles have been encouraging against *C. neoformans* including blood-brain barrier penetration. Toxicity comparison reveals variations, with ZnO and TiO_2 demonstrating favorable biocompatibility. Metal nanoparticles can serve as effective alternatives to traditional antifungal agents, particularly for drug-resistant and biofilm-associated infections. Their physicochemical versatility and ability to target various fungal structures favor their potential integration into next-generation antifungal strategies, pending further optimization to ensure safety and regulatory approval.

Keywords: Antifungal, Zinc oxide, Candida albicans, Reactive oxygen species, Drug resistance

1. Introduction

Candida albicans, *Aspergillus fumigatus*, and *Cryptococcus neoformans* are also responsible for fungal infections that have become a major and serious threat to the general population as well as immunocompromised people worldwide [1]. These opportunistic pathogens cause a wide range of clinical manifestations, including superficial mucocutaneous infections, but also highly morbid and fatal invasive systemic mycoses. The load is excessively heavy among patients receiving chemotherapy, organ transplantation, and living with HIV/AIDS, where the lack of immune surveillance contributes to the colonization of fungi, tissue invasion, and hematogenous spread [2]. One of this group of pathogens, *Candida albicans,* is the most commonly occurring pathogen in nosocomial fungi, and candidemia is currently one of the most common bloodstream infections in the intensive care unit. The most common etiological agent of invasive aspergillosis is *Aspergillus fumigatus,* which is a ubiquitous air mold with an associated mortality rate of over 50 percent in high-risk groups. The causative organism of cryptococcal meningitis responsible for causing tens of thousands of deaths annually, especially in resource-limited

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environments, is *Cryptococcus neoformans* due to its neurotropic behavior [3, 4].

Irrespective of developments in the modalities of diagnosis, early identification of invasive fungal infections (IFIs) has been less than ideal, which frequently leads to late therapeutic response and unfavorable clinical results. The five major classes of antifungal agents that are currently available are polyenes, azoles, echinocandins, allylamines, and flucytosine, whose use is limited by pharmacokinetic properties, toxicology, drug interactions, and toxic indices [5]. Furthermore, the development of multidrug-resistant fungi like *Candida auris* and azole-resistant *Aspergillus* species has additional complicated treatment regimens and highlighted the strong necessity to develop new antifungal approaches [6].

Nanotechnology, in this regard, has been receiving more and more focus as a revolutionary solution to antifungal treatment. Silver, copper, zinc oxide, titanium dioxide, and selenium-based metal nanoparticles are powerful antifungal agents acting via a variety of mechanisms, such as the production of reactive oxygen species, membrane destabilization, biofilm formation inhibition, and disruption of intracellular signaling [7]. Their large surface area-volume ratios, which can be tuned by physicochemical characteristics, and their ability to penetrate different cellular organelles make them attractive to overcome traditional drug resistance and attack fungal pathogens on various biological levels [8].

More recent developments in the green synthesis processes and biocompatible formulations have further increased the clinical uses of such nanomaterials, providing cost-effective, scalable, and environmentally friendly substitutes to conventional antifungals. Initial in vitro and in vivo data have indicated that they are effective against *Candida aspergillus* and *Cryptococcal* species, and are relatively noncytotoxic at therapeutic levels [9]. Nevertheless, there are still translational gaps, especially in the area of long-term safety, biodistribution, and regulatory approval pathways [10].

This review aims to provide a comprehensive and critical overview of the therapeutic potential of metal-based nanoparticles, such as Ag, Cu, ZnO, TiO_2, and Se, in relation to the three main pathogenic fungi of clinical interest. It will synthesize current epidemiological and pathophysiological knowledge of *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*, highlight the limitations of existing antifungal drugs and the rise of resistance, analyze the mechanisms and antifungal activity of the target nanoparticles, and explore future directions for translational research, clinical application. and regulatory integration. The goal is to clarify how nanotechnology can reshape antifungal therapy and address the unmet medical needs of invasive fungal infections through interdisciplinary contributions.

2. Methodology of literature selection

A systematic literature selection approach was used in this review to help it cover the uses of antifungals with metal-based nanoparticles comprehensively and in a relevant manner. Specific databases like PubMed, Scopus, and Web of Science were searched with specific keywords like metal nanoparticles, antifungal activity, *Candida, Aspergillus, Cryptococcus*, and biofilm inhibition to retrieve peer-reviewed articles published within 2010-2025. All original research articles, systematic reviews, and any in vivo study reporting on the mechanistic insight, comparative efficacy, or toxicity profiles were prioritized. Research papers were included depending on the importance and relevance to the three targeted fungal pathogens and concentration on silver, copper, zinc oxide, titanium dioxide or selenium nanoparticles. This method guaranteed a moderate synthesis of existing evidence along with scientific rigor and thematic focus.

3. Nanoparticle overview

The use of metal and metal oxide nanoparticles as effective antifungal agents has been achieved with the advantage of their unique physicochemical properties and a variety of mechanisms of action. These include silver, copper, zinc oxide, titanium dioxide, and selenium nanoparticles which have proven to be very effective against such pathogenic fungi as *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*.

Silver nanoparticles have been known to have broad-spectrum antimicrobial properties. They are usually less than 1 to 100 nanometers in size and are very reactive to the surface, hence they easily penetrate the fungal cells. These nanoparticles affect membrane integrity, form ROS, and disrupt essential cellular processes, so they will increase their therapeutic effect [11].

Copper nanoparticles are highly redox active, and are appreciated due to their cheapness and catalytic performance. They produce ROS, oxidize proteins and peroxidate lipids, which result in impaired cellular viability. They can be customized to be used in biomedical settings by their synthesis by chemical, thermal, or biological means [12].

Zinc oxide nanoparticles which are photocatalytic and semiconducting substances are usually prepared through sol-gel, hydrothermal or green synthesis

Table 1. Comparative overview of metal-based nanoparticles in antifungal therapy.

Nanoparticle	Antifungal efficacy	Biofilm inhibition	Toxicity profile	Notable targets	References
AgNPs	Very high against *Candida albicans* and *Aspergillus fumigatus*	Strong disruption of biofilm structure	Moderate to high cytotoxicity	*Candida*, *Aspergillus*, *Cryptococcus*	[13,7]
CuNPs	High against *Aspergillus fumigatus*	Moderate inhibition; strong ROS generation	High cytotoxicity; limited systemic use	*Aspergillus*	[17]
ZnONPs	High against *Candida albicans*	Strong biofilm penetration and membrane disruption	Low to moderate toxicity; good biocompatibility	*Candida*, *Aspergillus*	[13]
TiO_2NPs	Moderate to high (light-activated)	Effective under UV/visible light; ROS-mediated	Low toxicity; suitable for coatings	*Aspergillus*, *Candida*	[7]
SeNPs	Promising against *Cryptococcus neoformans*	Capsule disruption; moderate biofilm effect	Low toxicity; good CNS penetration	*Cryptococcus*	[22]

process. Their hexagonal wurtzite structure and small particles of about 50 nanometers or less are suitable in disrupting fungal biofilms and causing oxidative stress, thus making them suitable in topical and systemic use.

Titanium dioxide nanoparticles are commonly used in medical coatings and drug delivery systems. They are available in many different crystalline forms with anatase being the most biologically active. Exposed to both the ultraviolet or the visible light, these nanoparticles generate hydroxyl radicals and superoxide ions that damage membranes of the fungus and prevent the formation of biofilms. Their stability, non-toxicity and affordability only increase their popularity as antifungals [13, 14].

Selenium nanoparticles which have not been researched much are also earning their medicine through antimicrobial and antioxidant effects. They engage with the fungal biofilms and destabilize the cellular structures by changing the protein functioning, and eventually causing the death of cells. Their biocompatibility and low cytotoxicity make them very applicable in therapeutic applications especially in immunocompromised people [15].

The physicochemical properties of these nanoparticles directly affect their anti-fungal activity, i.e. size, surface charge, morphology and crystallinity. Smaller particles are better in cellular uptake and affinity to fungal membrane. Surface modification and elemental doping can further enhance their bioactivity and decrease their toxicity. These nanoparticles come in handy especially in drug-resistant strains and biofilm-related infections that are extremely hard to treat using standard antifungal treatment [16]. Table 1 highlights the antifungal action, biofilm inhibitory potential, toxicity of the five metal-based nanoparticles reviewed in this paper, and their pathogen-specific use.

4. Mechanisms of antifungal action

4.1. Oxidative stress and ROS-mediated damage

The antifungal effect of metal-based nanoparticles is credited to their small dimensions, large surface to volume ratio, and the availability to interrelate with the cells of fungus at various biological interfaces. The mechanism of action of these nanoparticles is a complicated one, and it involves the creation of oxidative stress, membrane integrity disruption, and disruption of the inner components. These processes are synergistic and the nanoparticles are able to circumvent the traditional resistance mechanisms. This makes them particularly useful with multidrug-resistant strains of fungi which can be exceptionally hard to treat through traditional treatment methods [17, 18]. One of the key processes that lead to the antifungal effect of metal-based nanoparticles is the creation of ROS, such as superoxide anions, hydroxyl radicals, and hydrogen peroxide. These reactive molecules cause oxidative stress in the fungal cells leading to lipid peroxidation, protein denaturation and nucleic acid fragmentation. These molecular perturbations impair cell integrity and cell viability [7]. In ROS generation, metal oxide nanoparticles, especially those of zinc oxide and titanium dioxide are the most effective. Titanium dioxide nanoparticles, in particular anatase crystalline form, improve the ROS generation under the influence of ultraviolet or visible light, and thus, increases their antifungal activity [17]. The damage that occurs due to ROS is particularly highly effective against fungal spores and the hyphal structures that are the key factors in fungal proliferation and invasion of tissues. The oxidative stress of *Aspergillus fumigatus* disrupts the mitochondrial activity and prevents conidia germination. The ROS disrupts the yeast-to-hyphae transition which is

Table 2. Quantitative comparison of ROS induction and EC_{50} values for metal-based nanoparticles.

Nanoparticle	ROS induction (fold increase vs. control)	EC_{50} range (μg/mL)	Biocompatibility summary
AgNPs	~3.5-fold in *Candida albicans*	25–80 μg/mL	High antifungal potency; moderate to high cytotoxicity.
ZnONPs	~2.8-fold in *Aspergillus fumigatus*	>100 μg/mL	Strong efficacy with favorable safety margin.
TiO_2NPs	Moderate (light-activated ROS)	>100 mg/L	Low toxicity; suitable for coatings and implants.
CuNPs	High ROS generation; redox-active	50–100 μg/mL	Strong antifungal effect; high cytotoxicity risk.
SeNPs	Moderate ROS; capsule disruption	Not consistently reported	Promising CNS targeting; low systemic toxicity.

a major determinant of pathogenicity and virulence in *Candide albicans* [9, 10]. Table 2 highlights the reported ROS induction levels and EC_{50} values of the five nanoparticles to support the mechanistic insights with quantitative evidence regarding their relatively effective and biocompatible performances.

4.2. Membrane disruption

Nanoparticles affect the integrity of fungal cell membranes with direct physical contacts as well as with electrostatic forces. Their tiny size of nanoscale facilitates their entry into the lipid bilayer causing the formation of pores, leakage of ions, and membrane potential disturbance. This structural injury usually occurs in the form of heightened permeability of membrane and leakage of cytoplasm which under electron microscopy is observed as collapsed cell walls and distorted cytoplasmic structure [19].

Nanoparticles of silver and copper demonstrate specific and high ability in destabilizing architecture of membranes because the nanoparticles are able to interact with thiol groups that are found on membrane proteins. This communication interferes with the protein activity and destabilizes membranes. Zinc oxide nanoparticles with a positive surface charge are strongly attracted by the electrostatic force to the negatively charged fungal membrane and hence increase the adhesion and cellular infiltration of nanoparticles [20].

4.3. Enzyme inhibition and DNA interaction

Other than compromising membrane integrity, the effects of nanoparticles on intracellular events have far-reaching impacts through reacting with its major biomolecules such as enzymes and nucleic acids. Silver nanoparticles are examples of nanoparticles that have been demonstrated to inhibit fungus enzymes that play an important role in cellular respiration and cell wall biosynthesis. This is made possible by the interaction of them with fungal DNA and enzymatic systems which lead to the error of replication, breakdown of metabolic balance and ultimately, cell cycle arrest, which results in the process of apoptosis-like cell death [21].

Enzyme-inhibitory properties are also exhibited by copper and selenium nanoparticles, mostly against catalase and superoxide dismutase are enzymes essential in reducing oxidative stress in fungal cells. The suppression of these defensive systems enhances the toxicity of reactive oxygen species, which increase the rate of cell damage and fungal cell death [22].

4.4. Species-specific considerations

Although the mechanisms mentioned above are mostly universal in fungi, certain structural and physiological peculiarities may affect the effectiveness of nanoparticle-based antifungal approaches.

The biofilm formation in *Candida albicans* is a major element of virulence and poses a major obstacle to antifungal infiltration. Metal nanoparticle has been shown to interfere with bi-film architecture and inhibit extracellular matrix formation to decrease biofilm biomass and metabolic activity. This property is especially useful in dealing with the infections of devices and stubborn cases of candidiasis [23].

Cryptococcus neoformans is defined as having a large polysaccharide capsule which prevents the activation of the immune system and restricts access to drugs. Nanoparticles can enter into this capsule and have antifungal effects in the cell. They damage the integrity of capsules, improving immune recognition and phagocytic clearance.

Thick cell wall and aerial hyphae in *Aspergillus fumigatus* presents a physical challenge to antifungal drugs. However, titanium dioxide and copper nanoparticles have demonstrated their ability to inhibit hyphal growth and spore germination, when exposed to light-activation conditions known to increase bioactivity [24].

Together, metal-based nanoparticles produce antifungal effects via several different mechanisms, such as oxidative stress, membrane disruption, ATP synthesis inhibition, and biofilm formation prevention. These multidrug measures make it possible to intervene selectively against various fungus, including

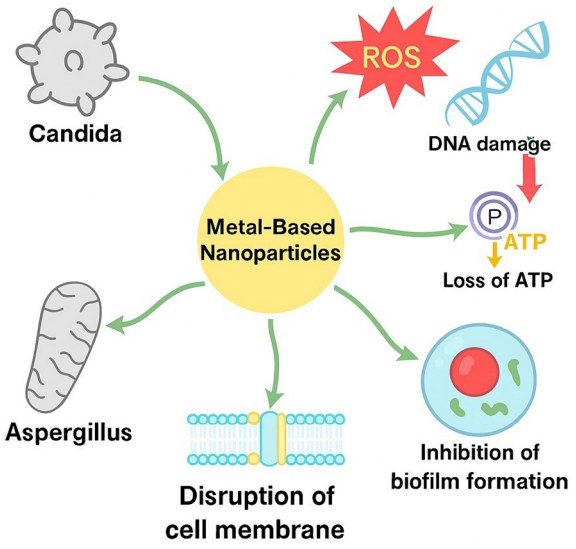

Fig. 1. Mechanistic targets of metal nanoparticles against fungal cells.

those having complicated resistance patterns. Fig. 1 Schematic model of the antifungal effect of metal-based nanoparticles on *Candida, Aspergillus, and Cryptococcus*. The nanoparticles cause oxidative stress, membrane disruption, ATP production impairment and biofilm formation inhibition [25].

5. Antifungal activity by pathogen

5.1. Candida albicans

Candida albicans is a polymorphic yeast which is able to form robust biofilms upon mucosal surfaces as well as medical equipment, which is associated with its pathogenicity and resistance to antifungal treatment [26]. These biofilms play the role of defense, protecting fungal cells against host immune response and pharmacological drugs by the formation of a thick extracellular matrix and by regulating the genes expression. The antibiofilm effect of nanoparticles has been shown to be significant due to its ability to interfere with matrix integrity and its ability to damage the fungal cell wall [27].

Silver nanoparticles have been one of the most widely studied to inhibit the formation of Candida biofilms. They are small with high surface reactivity that allows penetration of biofilms, augment membrane permeability, and cause oxidative stress, which promotes their fungicidal activities. Zinc oxide nanoparticles also possess a high affinity towards fungi membranes as a result of their positive charge upon the surface, which disrupts the cell wall and releases biofilm structures [28, 29].

Nanoparticles have been used in combination with standard antifungal agents and this combination has had some synergies leading to better therapeutic outcomes both against the drug-susceptible and drug-resistant strains. These combinations decrease minimal inhibitory concentrations and increase membrane targeting, therefore, increasing antifungal activity [30].

There is consistent experimental evidence of the capability of nanoparticles to prevent fungal growth, formation of biofilms, and virulence factor expression. These results are further confirmed in vivo, in which nanoparticle-based formulations have an important role in decreasing fungal burden and increasing survival rates. Topical applications have been found to have increased skin retention and therapeutic effectiveness over standard treatments [31].

Several studies have shown synergistic effects between metal-based nanoparticles and use of conventional antifungal agents, especially fluconazole and amphotericin B in treating *Candida albicans*. An example is when AgNPs were used in combination with fluconazole, antifungal activity was greatly increased, and MICs of fluconazole were reduced as much as 4-fold and biofilm integrity was interfered with better than with fluconazole alone [26, 30]. On the same note, ZnONPs have demonstrated synergies with amphotericin B, enhancing the permeability of the membrane and speeding the death of fungal cells in resistant organisms [29, 31].

At the same time, SeNPs co-administered with fluconazole decreased biofilm biomass by 60 percent and reinstated fluconazole sensitivity in fluconazole-resistant isolates of *C. albicans*. These synergetic activities are explained by the increased ROS production, greater uptake of drugs, and the blocking of fungal defenses by nanoparticles. These combinations have good prospects of defying the resistance to antifungal agents and lower the dose of standard medications, minimizing toxicity and enhancing clinical outcomes [27, 30].

5.2. Aspergillus fumigatus

Aspergillus fumigatus is a filamentous fungus which causes invasive aspergillosis, especially in immunocompromised patients. Airborne conidia and invasive presence of hyphae in the lung tissues are the main factors that provide it with pathogenicity. Nanoparticles have demonstrated significant possibilities of inhibiting spores' germination and causing structural damage to hyphae elements. Silver nanoparticles, particularly those produced biologically have been shown to inhibit fungal growth and cause ultrastructural changes such as membrane separation and

cytoplasmic leakage [32]. Their fungicidal effects can be further improved through plant-mediated synthesis, e.g. through neem extract methods, which induces deformation and growth inhibition of hyphae. Nanoparticles of titanium dioxide, especially in anatase crystalline structure, have antifungal effects that are light-activated by the synthesis of ROS, resulting in damage of the hyphae [33].

The capacity of nanoparticles to enter the fungal structures can be explained by the small size and high surface reactivity. Nanogel delivery systems including polyglycidol carriers that are loaded with antifungal agents have been taken up in fungal hyphae, enhancing drug delivery efficiency and decreasing cytotoxicity when compared to traditional formulations. Sustained release profiles are also provided by these systems, which makes them contribute to better therapeutic outcomes [34].

The most prominent process of antifungal activity is still the induction of oxidative stress. Nanoparticles (titanium dioxide and copper compounds) enhance the generation of ROS, overloading the defenses of the fungus antioxidant mechanisms and speeding up cell damage. ZnONPs xide can also play the role of oxidative stress and still have good biocompatibility [32].

The efficacy and safety of nanoparticle-based treatments have been proved by experimental studies. Silver nanoparticles biosynthesized with *A. fumigatus* as a biosensor have produced controlled particle sizes which have been shown to have antimicrobial activity and low cytotoxicity. Subsequent testing has indicated a low toxicity in the mammalian cell lines, which indicates that it can be used clinically [35].

In order to aid clinical translation, a number of in vivo studies have been conducted to find out the efficacy and safety of metal nanoparticles against *A. fumigatus*. ZnONPs or TiO_2NPs have demonstrated efficacy in reducing the fungal load and mortality in murine models of pulmonary aspergillosis with limited lung inflammation following therapeutic application of these nanoparticles. The evaluation of pulmonary toxicity shows that particle size, surface coating, and route of administration are key determinants affecting the biocompatibility and safety in the long term [32–34].

5.3. Cryptococcus neoformans

Cryptococcus neoformans is an encapsulated yeast that is the cause of the cryptococcal meningitis, a serious and usually deadly infection among the immunocompromised people. The polysaccharide capsule has a very tough obstacle to immune clearance and penetration of antifungal drugs and therapeutic intervention is especially difficult [36].

Nanotechnology provides a good option of disrupting the integrity of the capsule and enhancing intracellular drug delivery. Capsule biosynthesis and tissue invasion are specific fungal peptidases that have become potential molecular targets. Antifungal activity could be enhanced with nanoparticles that could destroy the structure of the capsules and inhibit these enzymes. Silver and selenium nanoparticles, e.g. have been shown to capture the components of capsules and cause oxidative damage [37].

However, efficient transport across the blood-brain barrier (BBB) is also a key challenge. Specific fungal metalloproteases help CNS to be invaded implying that nanoparticle formulations that replicate or disrupt these effects may improve central nervous system targeting. Antifungal-loaded functionalized alginate nanoparticles have demonstrated the ability to cross over the BBB and decrease fungal burden in the brain tissue causing no toxicity [38].

Another new approach is exosome-based delivery systems. Exosomes engineered have been able to deliver amphotericin B into the brain with a minimal nephrotoxicity. In the same manner, the complexes of gold nanoparticles have demonstrated superior fungal clearance effect and long half-life over traditional formulations. Also, the synthetic host defense mimic, brilacidin, has shown effective antifungal action against *C. neoformans*, interrupting membrane integrity, and increasing the action of conventional antifungals [39,40].

The recent research has investigated innovative nanocarrier systems that can be used to cross blood-brain barrier and increase antifungal drug delivery to central nervous system. The nanoparticles of selenium and lipid-coated metal nanocarriers have been shown to have better CNS-accumulation, reduced fungal burden, and desirable neurotoxicity in murine models of cryptococcal meningoencephalitis. The results confirmed the potential of nanoparticle-based therapies in the treatment of *Cryptococcus neoformans* to become translationally applicable, primarily in overcoming the capsule-mediated resistance and the BBB restrictions [36-39].

6. Comparative Analysis

The development of metal and metal oxide nanoparticles has become a viable option for antifungal agents with respect to their distinctive physicochemical characteristics and multimodal actions. In this part, a comparative analysis of nanoparticles

Table 3. Comparative properties of metal-based nanoparticles in antifungal applications.

Nanoparticle	Target fungi	Mechanism	Effective dose	Toxicity	Key findings	References
AgNPs	*Candida, Aspergillus, Cryptococcus*	ROS generation, membrane disruption, DNA interaction	25–62.5 μg/mL	Moderate (EC_{50} ~11.3 mg/L in mammalian cells)	Broad-spectrum efficacy; biofilm inhibition; synergism with azoles	[22]
CuNPs	*Candida, Aspergillus*	ROS, protein oxidation, membrane damage	50–100 μg/mL	Moderate to high (EC_{50} ~25 mg/L)	Effective against hyphal forms; penetrates fungal structures; induces oxidative stress	[17]
ZnONPs	*Candida, Aspergillus*	ROS, cell wall disruption, biofilm inhibition	30–80 μg/mL	Low to moderate (EC_{50} ~43 mg/L)	Strong antibiofilm activity; synergistic with fluconazole; low cytotoxicity	[8]
TiO_2NPs	*Candida, Aspergillus*	Photocatalytic ROS, membrane destabilization	100–200 μg/mL (light-activated)	Low (EC_{50} >100 mg/L)	Effective under UV/visible light; stable and biocompatible; surface coating potential	[32,33]
SeNPs	*Candida, Cryptococcus*	Sulfur substitution, capsule disruption, antioxidant modulation	50–100 μg/mL	Low to moderate	Targets biofilm and capsule; minimal cytotoxicity; promising CNS delivery formulations	[22,13]

against *Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans* with regard to their mechanisms, effective doses, toxicity profile, and major findings is presented.

A summary of the important antifungal properties of the metal-based nanoparticles concerning their respective target fungus, mode of action, dose ranges of efficacy, toxicity, and significant therapeutic results is given in Table 3. This comparative review demonstrates the variety and the opportunities of the nanoparticle-based methods in the fight against these fungi.

6.1. Mechanistic comparison

The most varied mechanisms demonstrated by the AgNPs are ROS generation, membrane disruption as well as interaction with DNA. They are small in size and highly reactive to surfaces which allows them to penetrate fungal cells and biofilms. CuNPs mainly cause oxidative stress and oxidation of proteins, which is effective on hyphae structure of *Aspergillus fumigatus* [32]. ZnONPs disperse through fungal membranes and biofilms by using ROS and electrostatic interactions, whereas TiO_2NPs by using photocatalytic properties to produce hydroxyl radicals when exposed to light. SeNPs interfere with the functioning of proteins and capsule integrity of *Cryptococcus neoformans* by replacing sulfur in amino acids [41].

6.2. Effective dose and toxicity

At relatively low doses (25–80 μg/mL), AgNPs and ZnONPs possess high antifungal activity, but display moderate toxicity. Silver nanoparticles are highly potent but linked with lower EC_{50} of mammalian cells, which shows that they have a narrower therapeutic index. However, ZnONPs show less cytotoxicity, which provides a better safety margin [20]. Similarly, CuNPs can also be used in the 50-100 0g/mL range, but their strong redox potential makes them more prone to high cytotoxicity and hence reduces their usefulness in sensitive biological applications. One of the least toxics is titanium dioxide nanoparticles with an EC_{50} of more than 100 mg/L, which makes them acceptable in surface finishes and implantable bio devices. SeNPs offer a promising compromise between antifungal potency and biocompatibility especially when it comes to antifungal preparations with central nervous system targeting. Their physicochemical properties and less toxic nature make them convincing agents of further-therapy to treat fungi-related infections [11].

6.3. Pathogen-specific insights

6.3.1. Nanoparticle-based antifungal strategies: Comparative insights across pathogens

Nanoparticles have proved to be multifunctional agents in antifungal therapy with specific benefits

Table 4. Therapeutic properties and biological limitations of antifungal nanoparticles.

Nanoparticle	Target pathogen(s)	Key advantages	Limitations	References
AgNPs	*Candida*, *Aspergillus*, *Cryptococcus*	Broad-spectrum activity, biofilm inhibition	Moderate toxicity, dose-sensitive	[22,32]
ZnONPs	*Candida albicans*	Potency with reduced toxicity	Limited CNS penetration	[8,33]
CuNPs	*Aspergillus fumigatus*	Strong antifungal effect	High cytotoxicity	[8,17]
TiO_2NPs	*Aspergillus fumigatus*	Low toxicity, surface stability	Limited systemic application	[32,33]
SeNPs	*Cryptococcus neoformans*	CNS delivery, capsule penetration	Requires formulation optimization	[22,13]

over pathogens and the properties of traditional medicines. They can be specifically disrupted by their physicochemical properties, targeting fungal structures and biofilms, and have different compatibility profiles, depending on the formulation and clinical use.

- *Candida albicans*: AgNPs and ZnONPs prove to be very effective in the prevention of biofilm formation as a major virulence factor triggered by Candida infection. These nanoparticles were also found to enhance the activity of azole anti-fungal causing significant decreases in minimum inhibitory concentrations. ZnONPs in specific have an excellent safety profile, which means that they can be used as mucosal and systemic agents [27].
- *Aspergillus fumigate*: CuNPs and TiO_2NPs have a high antifungal effect on spores and on hyphae. At moderate concentrations, AgNPs have been demonstrated to cause ultrastructural damage as well as to inhibit fungal growth. CuNPs are very powerful but they are also very toxic to human cells, so care should be exercised. With their chemical stability and low toxicity, TiO_2NPs are suitable in surface coating of the environment and implants [32].
- *Cryptococcus neoformans*: SeNPs and AgNPs have the capacity to enter the polysaccharide capsule and disrupt the intracellular processes. SeNP-based preparations are reported to have penetrated the blood-brain barrier and reduced fungal burden of central nervous system models, which reflect their promise in the treatment of cryptococcal meningitis [42].

To conclude, Table 4 presents the principal attributes of five classes of metal nanoparticles in controlling fungi in terms of their antifungal properties, their therapeutic properties, and the drawbacks of their biological application.

The results highlight the necessity of selecting nanoparticles with respect to fungal species and the therapeutic environment. Whereas being broad-spectrum, AgNPs have alternatives in ZnONPs and SeNPs that are safer to use in a particular infection. CuNPs and TiO2NPs are potent, but only localized interventions or surface interventions should be referred to. Despite their effective antifungal effects especially against *Aspergillus fumigatus*, CuNPs have a high cytotoxicity thus restricting their systemic therapeutic use. In an attempt to mitigate this issue; low-dose composite preparations, fungal surfacing, and localized delivery (e.g. topical use or as device coatings) have been suggested in order to preserve antifungal activity whilst reducing host toxicity [41, 42].

7. Toxicity and biocompatibility

Although metal and metal oxide nanoparticles like Ag, Cu, ZnO, TiO_2, and Se have potent antifungal activity, their biomedical usage must carefully be considered in regards to cytotoxicity and biocompatibility. The therapeutic window of these nanomaterials is determined by the capacity of the nanomaterial to selectively attack fungal cells and reduce the side effects on host tissues. This section is the critical discussion of cytotoxic responses on human cell lines, dose-dependent safety and the new strategies to increase selectivity and decrease host toxicity.

7.1. Cytotoxicity in human cell lines

7.1.1. In vitro cytotoxicity profiles of metal-based nanoparticles

Cytotoxicity assays on several cell lines of humans have shown that there are different biological responses to metal-based nanoparticles and that dosage optimization and cell-type specificity is vital in treatment procedures.

Silver nanoparticles are reported to cause oxidative stress and apoptosis of human cells in several cell types, such as hepatocytes, lung fibroblasts, and keratinocytes. Ag-doped titanium dioxide (Ag_2O_2-TDO) nanoparticles increase further the production of ROS, and the depletion of intracellular antioxidants, especially in hepatic cells, the toxicity being higher with increased doping. Also, AgNPs have been linked to lower glutathione and high levels of nitric oxide and superoxide dismutase suggesting oxidative damage at the systemic level [43].

Zinc oxide nanoparticles show dose-dependent cytotoxicity, especially in the human aorta smooth muscle cells. They cause their toxicity through accumulation of intracellular ROS and endoplasmic reticulum stress, in addition to the upregulation of stress biomarkers, including DDIT3 and phosphorylated Chop. Moreover, ZnONPs induce inflammatory reactions by releasing more soluble adhesion molecules, such as VCAM-1 and ICAM-1 [44].

Copper oxide nanoparticles although have strong antimicrobial effects, they are more cytotoxic compared to ZnONPs and TiO_2NPs, at the same concentration. The main cause of this increased toxicity is redox cycling and copper ions release which interferes with cellular homeostasis and facilitates oxidative damage [45].

Titanium dioxide nanoparticles are not the most cytotoxic of the formulations tested, so they can be used in applications related to coating surfaces and implantable devices. The minimal ion release and chemical stability of the material form the basis of a favorable biocompatibility profile [46].

Selenium nanoparticles are unique as their cytotoxicity is not much in normal human cells. They have inherent antioxidant properties and are able to regulate oxidative stress signaling, which gives them a protective effect, especially with regard to the neural and epithelial cell lines. These qualities make SeNPs good candidates in antifungal therapy of the systemic and central nervous system [47].

7.1.2. Dose-dependent cytotoxicity and safety profiles of nanoparticles

Nanoparticle-induced cytotoxicity is dose-dependent in nature and often has a sigmoidal dose-response relationship. This pharmacodynamic feature requires the control of the concentration to be fine-tuned so as to achieve a balance between therapeutic efficacy and cell safety.

Comparative studies of nanoparticles on intestinal epithelial cell models have identified a toxicity hierarchy of the most widely studied nanoparticles. Silver nanoparticles with the coating of polyvinylpyrrolidone (PVP) are the most cytotoxic, and silver, copper oxide, and zinc oxide and titanium dioxide are next. The EC_{50} values are a large range, between the microlamoles per gram and concentrations in the order of 100 mg/L, which demonstrates the importance of surface functionalization and colloidal stability to reduce the negative impact [48].

TiO_2NPs and in particular anatase form are characterized by the low cytotoxicity at therapeutic doses. The fact that they are chemically inert and release few ions, allows them to be used in biomedical applications, such as implant coating and drug delivery interfaces. TiO_2 is capable of producing reactive oxygen species in a regulated way, under the stimulus of visible light, and can expand the antimicrobial effects without damaging the integrity of the host cells [49].

The safety profile of selenium nanoparticles is also quite favorable, and low cytotoxicity levels are identified at the concentration needed to treat fungal pathogens. They have intrinsic antioxidant properties as well as the capacity to tune the oxidative stress pathways which make them biocompatible. Their use in systemic and CNS-targeted antifungal preparations can be validated using a wide variety of in vitro and in vivo models [50].

This results in the need to emphasize the critical role of nanoparticle engineering, especially surface modification, dose accuracy, and physicochemical optimization, in the attainment of safe and effective therapeutic outcomes.

7.2. Strategies to enhance safety and selectivity of nanoparticle-based antifungal therapies

To reduce host toxicity and maximize therapeutic specificity, a plethora of nanoparticle engineering methods has been created, and all of them result in improved safety profile and enhanced antifungal activity. Surfaces functionalization wherein non-specific cellular interactions and systemic circulation lengthening can be diminished by enveloping nanoparticles with biocompatible polymers such as polyethylene glycol (PEG), chitosan or albumin. These surface alterations allow the fungal cells to selectively adopt them and reduce the off-targets to mammalian tissues [51].

- Selective ligand targeting: therapeutic selectivity: nanoparticles can be modified with selective ligands thus enabling fungal surface markers to be targeted with a high degree of therapeutic selectivity. Particularly active nanoparticles conjugated with Mannan novel biomaterials exploit the effects of Candida biofilms killing and can be used to capitalize on iron-deprivation minigenic effects in fungal micro environments to enhance cellular internalization [52].
- The drugs can be absorbed in liposomes or in biodegradable polymeric matrices in controlled release formulations where the drugs are gradually released to minimize peaks in cytotoxicity of the drug concentration. This enables the provision of a stable therapeutic presence and decreases the systemic toxicity, especially in sensitive tissues such as the kidney and central nervous system [53].

- Possibly to achieve this, the trace elements (silver) can be incorporated into either the titanium oxide or the zinc oxide matrix, where the desired generation of reactive oxygen species (ROS) can be finely tuned. It is possible to specifically induce apoptosis of the pathogenic cells but not compromise the integrity of healthy host tissues using these composite nanoparticles [49].

7.3. Limitations and translational considerations

Although the antifungal properties of metal-based nanoparticles have been clearly proven by means of in vitro research, there are a several shortcomings that have to be admitted when projecting the results to the clinical practice. The complexity of host-pathogen interactions and immune responses, as well as tissue-specific pharmacokinetics that affect therapeutic outcomes in vivo are usually not modeled in vitro. Nanoparticle aggregation, protein corona formation, and changes in the biodistribution are some of the factors that can profoundly influence the efficacy and toxicity profiles under non-controlled laboratory conditions. In addition, concentrations necessary to produce antifungal effects in vitro might be imprecisely predictable into effective and safe doses in human systems, especially, due to the possibility of cytotoxicity and accumulation in specific tissues. Reproducibility and regulatory evaluation are further compromised because of the absence of standard protocols to synthesize and characterize nanoparticles and also to perform biological tests. The future research should focus on the well-designed in vivo studies, such as pharmacodynamic modeling, long-term toxicity testing, and nanoparticles behaviors in the complex biological conditions to bridge this translational gap. To make it more relevant to clinical practice, it is also worth considering integration of sophisticated delivery methods, e.g., functionalized carriers or BBB-penetrating formulations.

8. Clinical and translational potential

Metal and metal oxide nanoparticles including silver, copper, zinc oxide, titanium dioxide, and selenium as therapeutic agents against fungal pathogenic organisms *Candida albicans*, *Aspergillus fumigatus,* and *Cryptococcus neoformans* have developed in vitro research into translational preparations and preclinical models. Their physicochemical versatility has allowed them to be incorporated into a vast diversity of delivery vehicles, such as topical gels, implantable surfaces, nanocarriers and exosome-based chasses, with significant antifungal efficacy and biocompatibility [54].

The strategies of the recent formulations have focused on the introduction of these nanoparticles into biocompatible matrices to improve physicochemical stability, specificity in targeting, and controlled drug release. Silver and zinc oxide nanoparticles are also incorporated into hydrogel and polymeric film to be applied topically especially in chronic wound healing and in mucosal candidiasis [55]. Due to their photocatalytic properties and low-toxicity, titanium dioxide nanoparticles have been intensively applied to medical devices as antimicrobial coatings, providing long-term protection against the microbial adhesion and biofilm formation. The central nervous system-targeted delivery with selenium nanoparticles was first considered, especially in the therapy of cryptococcal infections, and the developed formulations exhibit effective penetration into the blood-brain barrier and lower systemic toxicity [56].

The antifungal activity of metal-based nanoparticles in preclinical studies has been supported by the results of improvement in survival and fungal burden in systemic and topical infections in animals, as well as, in laboratory experiments. Despite the fact that clinical translation has been early and slow, there is a progressive trend as nanoparticle platforms that were initially used in antibacterial and oncological applications are considered in antifungal use, particularly in the situations associated with drug resistance and biofilm-related pathology. Combinatorial options, e.g. the co-administration of nanoparticles with antioxidants have proved to be advantageous in reducing cytotoxicity without compromising antifungal efficacy [57].

Although these developments have been made, the regulatory authorization of nanoparticle-based antifungal medicines should be subject to overcoming several major issues concerning long-term safety, biodistribution, and environmental fitness, as well as uniformity in production. Toxicological profiling and standard characterization procedures are needed by regulatory agencies, and are in development [58]. The future of this area lies in customization of nanomedicine in respect of pathogen type and host, development of multi-functional systems that combine therapeutic and diagnostic functions, green synthesis processes to reduce ecological and biological hazards and design of coordinated international guidelines to enable clinical integration [59].

9. Challenges and future perspectives

Although the metal and metal oxide nanoparticles, including silver, copper, zinc oxide, titanium dioxide and selenium, show significant potential antifungal effects on fungal pathogens, i.e. *Candida*

Table 5. Comparative therapeutic profiles and translational prospects of metal-based nanoparticles in antifungal applications.

Nanoparticle type	Target fungi	Therapeutic efficacy	Cytotoxicity profile	Current applications	Key challenges	Future directions
AgNPs	*Candida*, *Aspergillus*, *Cryptococcus*	Broad-spectrum activity, biofilm inhibition, synergy with azoles	Moderate; dose-dependent oxidative stress	Polymeric films, albumin nanocarriers, topical gels	Dose optimization, host toxicity	Combination with antioxidants, targeted delivery systems
ZnONPs	*Candida albicans*	Effective against biofilms, enhances azole efficacy	Lower than AgNPs; induces ER stress and inflammation	Hydrogels, topical formulations	Limited CNS penetration, inflammatory response	Localized applications, improved biocompatibility
CuNPs	*Aspergillus fumigatus*	Strong antifungal activity against spores and hyphae	High; redox activity and ion release	Experimental formulations	Elevated cytotoxicity	Low-dose composites, selective targeting
TiO_2NPs	*Aspergillus*, surface-level infections	Stable, photocatalytic, anti-biofilm properties	Minimal; especially in anatase form	Medical device coatings, implantable surfaces	Limited systemic use, activation requirements	Smart coatings, light-activated antimicrobial platforms
SeNPs	*Cryptococcus neoformans*	Capsule penetration, CNS-targeted efficacy	Low; antioxidant properties, high biocompatibility	Polysorbate-functionalized carriers, exosome systems	BBB penetration, formulation scalability	CNS-directed nanomedicine, systemic antifungal therapies

albicans, Aspergillus fumigatus and Cryptococcus neoformans, several translational issues exist that need to be overcome to achieve safe and effective clinical application. The challenges include lack of standard antifungal testing procedures, complicated delivery of the drugs in central nervous system and systemic infections, necessity of combining it with some antifungal regimen, and increasing concerns of ethics and environment regarding the use of nanoparticles [31, 60].

One of the biggest challenges facing antifungal research using nanoparticles is a lack of harmonized testing procedures. The traditional susceptibility assays, which have been developed to be sensitive to small-molecule drugs, have not usually taken into consideration the special physicochemical characteristics of nanoparticles. The aggregation behavior, kinetics of ion release, and surface charge may greatly affect the results of the assays, so it is important to create specific protocols that capture the dynamics unique to nanoparticles. Also, there is variability in synthesis and characterization across different laboratories making comparative efficacy testing difficult, and therefore there should be consensus guidelines standardizing media composition, inoculum density, and endpoint criteria [33, 61].

The limitation is a characteristic of the blood-brain barrier that makes the adequate treatment of cryptococcal meningitis especially difficult. The systems delivery involving nanoparticles can be quite a promising solution to the problem and to achieve the successful transition, the physiological and pharmacokinetic obstacles have to be approached. Advanced platforms of nanoparticles including liposomes, dendrimers, exosomes, and membrane-engineered nanoparticles have been demonstrated to provide enhanced targeting to the CNS through receptor-mediated transcytosis and intrathecal delivery. However, scalability, biodistribution consistency and clearance dynamics also remain as a considerable obstacle that must be surmounted in order to attain therapeutic reliability [45, 62].

One of the opportunities to enhance the performance and counteract resistance is the combination of nanoparticles with conventional antifungal drugs. Synergistic interactions have been observed to have the potential of interfering with fungal membranes by metal nanoparticles in combination with drugs such as amphotericin B and azoles to increase drug uptake particularly in infections caused by biofilm and drug-resistant strains. Pharmacodynamic interactions, as well as toxicity profiles, however, need to be considered attentively. Nanoparticles synthesized in green and with reduced toxicity and compatibility have a good future, although they have to pass stringent in vivo tests in an endeavor to justify their application in clinics [47, 51].

The use of metal nanoparticles is also coupled with the rising number of ethical and environmental concerns. They are capable of intruding into the microbial abodes in their subsistence of the soil and water systems as well as aiding in the emergence of resistance through horizontal gene transfer. There are also more environmentally friendly ways of

sustainable synthesis through the assistance of biological systems, which reduce the wastes and promote biocompatibility. The regulatory frameworks must be transformed to advance pragmatic innovation to fulfill the lifecycle management of nanoparticles including disposal, environmental monitoring, and protracted safety assessments [49, 63].

Metal and metal oxide nanoparticles have a great potential in antifungal therapy but clinical usage of nanoparticles requires solution to major scientific, regulatory, and ethical issues. Their therapeutic potential will demand development of standardized testing, targeted delivery, combinatorics and long-term development. Table 5 provides a comparative description of the notable metal and metal oxide nanoparticles in antifungal therapy in terms of their target specificity, therapeutic potential, cytotoxicity profiles, current applications, and challenges concerning translational applications, and future directions.

10. Conclusion

CuNPs, ZnONPs, TiO_2NPs and SeNPs have been found to exhibit high antifungal activity against *Candida albicans, Aspergillus fumigatus and Cryptococcus neoformans* by a number of different mechanisms that circumvent conventional drug resistance strategies. They may also result in biofilm destruction, fungal invasion and may also work synergistically with the already available antifungals and therefore are also good candidates in the next-generation therapeutics. They are AgNPs and ZnONPs with the capability to perform in a wide-spectrum and SeNPs with the possibilities of the CNS-targeted application due to their biocompatibility. Even though preclinical research has been promising, clinical translation requires standardized tests, streamed delivery vehicles, and harmonization of regulations. The future studies ought to deal with hybrid nanocarriers, biofunctionalized surface coating of medical equipment, and clinical trials involving humans on CNS based therapies. Such instructions will close the existing gap between laboratory and clinical practice, and lead to a higher level of accuracy and safety in nanoparticle-based antifungal plans.

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Conflict of interest

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