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Review

A comprehensive review on potential applications of metallic nanoparticles as antifungal therapies to combat human fungal diseases

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ABSTRACT

Human pathogenic fungi are responsible for causing a range of infection types including mucosal, skin, and invasive infections. Life-threatening and invasive fungal infections (FIs) are responsible for mortality and morbidity, especially for individuals with compromised immune function. The number of currently available therapeutic agents against invasive FIs is limited compared to that against bacterial infections. In addition, the increased mortality and morbidity caused by FIs are linked to the limited number of available antifungal agents, antifungal resistance, and the increased toxicity of these agents. Currently available antifungal agents have several drawbacks in efficiency, efficacy, toxicity, activity spectrum, and selectivity. It has already been demonstrated with numerous metallic nanoparticles (MNPs) that these nanoparticles can serve as an effective and alternative solution as fungicidal agents. MNPs have great potential owing to their intrinsic antifungal properties and potential to deliver antifungal drugs. For instance, gold nanoparticles (AuNPs) have the capacity to disturb mitochondrial calcium homeostasis induced AuNP-mediated cell death in *Candida albicans*. In addition, both copper nanoparticles and copper oxide nanoparticles exerted significant suppressive properties against pathogenic fungi. Silver nanoparticles showed strong antifungal properties against numerous pathogenic fungi, such as *Stachybotrys chartarum*, *Mortierella alpina*, *Chaetomium globosum*, *A. fumigatus*, *Cladosporium cladosporioides*, *Penicillium brevicompactum*, *Trichophyton rubrum*, *C. tropicalis*, and *C. albicans*. Iron oxide nanoparticles showed potent antifungal activities against *A. niger* and *P. chrysogenum*. It has also been reported that zinc oxide nanoparticles can significantly inhibit fungal growth. These NPs have already exerted potent antifungal properties against a number of pathogenic fungal species including *Candida*, *Aspergillus*, *Fusarium*, and many others. Several strategies are currently used for the research and development of antifungal NPs including chemical modification of NPs and combination with the available drugs. This review has comprehensively presented the current and innovative antifungal approach using MNPs. Moreover, different types of MNPs, their physicochemical characteristics, and production techniques have been summarized in this review.

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1. Introduction

In humans, fungal infections (FIs) are responsible for causing a wide range of diseases ranging from skin infections to life-threatening invasive FIs (Bongomin et al., 2017; Brown et al., 2012; Fisher et al., 2022). So far, approximately 300 fungal species have been found to result in various fungal diseases in humans (Wall and Lopez-Ribot, 2020). Worldwide, pathogenic fungi are responsible for approximately 1.5 million deaths and 13 million FIs per year, where most of the affected people have compromised immune function (Rayens and Norris, 2022). Unfortunately, the number of affected cases has been increasing continuously (Houšť et al., 2020). Furthermore, FIs are linked to increased rates of mortality and morbidity (Kainz et al., 2020). FIs are also a major concern for clinicians owing to their increased occurrence rate, particularly in immunocompromised individuals. Various factors play roles in determining the increased occurrence rate of FIs, including organ transplantation, the use of immunosuppressive anticancer drugs, parenteral nutrition, treatment with corticosteroids, hemodialysis, the prolonged use of urethral and intravascular catheters, the long-term use of broad-spectrum antibiotics, and host immunity (Dos Santos Ramos et al., 2018).

Early diagnosis and treatment are crucial factors in effective antifungal therapy. In addition, adjunctive therapies and the surgical removal of all of the infected tissues are important to eliminate mucormycosis; for instance, amphotericin B (AmB) is effective in treating mucormycosis (Skiada et al., 2018). Other antifungal drugs include triazoles such as voriconazole, isavuconazole, and posaconazole. However, the emergence of antifungal resistance is an enormous clinical challenge for clinicians because of the limitations of currently available antifungal agents (AFAs). For example, elevated levels of resistance to echinocandins and azoles in various non-albicans *Candida* species and resistance to azoles in *the* pathogenic filamentous fungus *Aspergillus fumigatus* (*A. fumigatus*) have been observed. This may be due to environmental or clinical exposure to these AFAs. Moreover, multiple species of fungal pathogens have already developed resistance or show decreased susceptibility to numerous AFAs that are currently available.

Nanotechnology is the study and modification of the properties of substances by regulating their sizes (Nayak et al., 2016). In recent times, nanotechnology innovations have emerged as effective approaches in overcoming drug resistance (Lima et al., 2019). It has already been demonstrated that nanotechnology-based antimicrobial agents show improved flexibility, strength, performance, and durability, in addition to unique physicochemical properties (Z. Wu et al., 2022). There is a growing interest in nanoparticles (NPs) owing to their shape, size, and high surface area (Nayak et al., 2016) Nanoparticles (NPs) are small particles and their size ranges between 1 nm and 100 nm (Joseph et al., 2023). NPs have various exceptional properties including a macroscopic quantum tunnelling effect, a quantum size effect, an optical effect, and a surface effect. Several properties of NPs, including sensitivity, catalysis, magnetism, electricity, light, and heat, differ from conventional materials. NPs are classified based on their sizes, shapes, and properties, for example- metallic NPs (MNPs), polymeric NPs, fullerenes, and many more (Joseph et al., 2023). NPs can be synthesized by using biological, physical, and chemical methods. Physical and chemical methods are most commonly used to synthesize NPs. However, there is growing interest in green synthesis and this approach is increasingly being used to produce environmentally safe and nontoxic NPs (Adibian et al., 2022; Foroutan et al., 2022; M. Hasanin et al., 2022b).

NP-based drug delivery systems provide a potential alternative to develop newer pharmaceutical formulations in order to effectively fight against FIs and overcome the fungal multi-resistance to currently available AFAs (León-Buitimea et al., 2021). In nanomedicine, NPs are extensively used against fungal and bacterial infections, owing to the lower chance of pathogens in developing resistance against the NPs. Furthermore, a range of NPs exhibit effective antifungal properties and have the potential to be regarded as an alternative to treat various FIs (Shaikh et al., 2019). In particular, metal NPs exhibit potent antifungal properties (Shaikh et al., 2019). The success of nanoparticulate systems as drug carriers depends on the success of selective, stable, and biocompatible NPs that could be delivered to specific areas in the body via systemic administration with low toxicity and good safety. Present antifungal nanomaterials are divided into three major groups including organic nanostructures, inorganic NPs, and hybrid nanostructures (Xia et al., 2016). Inorganic NPs primarily comprise MNPs and semiconductor nano-ions with photocatalytic activity (Xu et al., 2021).There is growing interest in MNPs because of their novel size-dependent properties and behaviour. In addition, it has been demonstrated that MNPs are effective as stable and suitable targeting tools for the sustained and controlled release of drugs. MNPs are also nontoxic, inert, and biocompatible. They can also easily be produced with various size ranges, alongside their ease of surface functionalization and low dispersity index. Collectively, these features offer optimal ligand density on the surface at the low core diameter size; thus, MNPs have the potential to serve as appropriate and auspicious targets for drug delivery systems (DDSs). Various other advantages of MNPs (especially metal oxides) include their diverse applications, their good

Table 1
Overview of common fungal infections.

Fungal diseases	Fungal Species	Clinical manifestations	Traditional antifungal therapy	References
Aspergillosis	Aspergillus species	Fever; dyspnea; cough; subacute invasive pulmonary aspergillosis; cavitary tuberculosis	Polyenes, echinocandins, and azoles	(Latgé and Chamilos, 2020)
Blastomyscosis	Blastomyces dermatitidis	Fever; night sweats; anorexia; malaise; weight loss; hemoptysis; persistent cough	Polyenes and azoles	(McBride et al., 2017)
Candidiasis	Candida species	Fever; polymyalgia; chills; polyarthralgia; retinal exudate; candidemia; candida infection of the esophagus, vagina, mouth, and throat; tenosynovitis; septic arthritis, meningitis; endophthalmitis; infective endocarditis	Polyenes, echinocandins, and azoles	(Du et al., 2021)
Coccidioidomycosis	Coccidioidis immitis	Arthralgias; fever; pleuritic pain; cough; profound fatigue; headache; meningitis	Polyenes and azoles	(Garcia Garcia et al., 2015)
Paracoccidioidomycosis	Paracoccidioidis brasiliensis	Malaise; fever; dyspnea; cough; pulmonary hypertension; pulmonary bullae; pulmonary fibrosis	Polyenes and azoles	(Peçanha et al., 2022)
Cryptococcosis	Cryptococcus neoformans	Fever; headache; signs of meningeal irritation; memory loss; lethargy; altered mentation; cranial neuropathies	Polyenes, azoles, and 5-fluorocytosine	(Molloy et al., 2018; Mourad and Perfect, 2018)
Histoplasmosis	Histoplasma capsulatum	Fever; headache; weakness; malaise; dry cough; sweats; pleuritic chest pain; dyspnea	Azoles and polyenes	(Lakhani et al., 2019)
Talaromycosis (penicilliosis)	Penicillium marneffei	Skin lesions; lymphadenopathy; anemia; weight loss; fever	Azoles and polyenes	(Wang and Deng, 2021)

selectivity, their recyclability, and an increased level of catalytic function (Kharisov et al., 2019). Numerous studies have already confirmed that NPs exhibit increased efficiency, enhanced antimycotic stability and solubility, do not produce drug resistance, greater selectivity for the infection site, and show present fewer side effects (Bhatt et al., 2018; Escárcega-González et al., 2018; León-Buitimea et al., 2021; Pelgrift and Friedman, 2013; RubenMorones-Ramirez et al., 2013; Sousa et al., 2020). Numerous MNPs and metal oxide NPs including gold (Au), silver (Ag), copper oxide (CuO), silica (Si), magnesium oxide (MgO), calcium oxide (CaO), zinc oxide (ZnO), titanium dioxide (TiO_2), and silver oxide (Ag_2O) have already demonstrated their antimicrobial activities (Dizaj et al., 2015). Multiple studies have already confirmed that MNPs can be efficiently utilized against many fungal pathogens. Based on the latest scientific literature, this review has provided an overview of FIs, current AFAs, the potential applications of MNPs as AFAs, and their production methods and physicochemical characterization. This review particularly aimed to comprehensively discuss the antifungal activities of a range of MNPs against fungal pathogens.

2. Fungal infections in humans

Human FIs are markedly different from other infections. Fungi, as eukaryotic pathogens, share numerous similarities with their host cells (Rodrigues and Nosanchuk, 2020). Fungi that cause infections in humans need to satisfy four major characteristics including the need to evade the human immune system, the capacity to obtain their own nutrition by digesting and absorbing elements of human tissues, the capacity to reach the tissues linked to their pathogenesis, and the capacity to grow at or above 37 °C. Fungi that meet the aforementioned criteria can produce various infections ranging from mucosal and skin infections to life-threatening invasive FIs, and approximately 30 species are responsible for over 99% of infections. Even though several fungal species are capable of triggering infections in healthy people who are immunocompetent, most fungal species are opportunistic pathogens and require a susceptible host. It has been reported that successful treatment of severe underlying diseases and advances in modern medicines have resulted in an increased number of immunosuppressed people and medically compromised individuals who are naturally vulnerable to these devastating FIs (Wall and Lopez-Ribot, 2020).

There are multiple risk factors that play an important role in the development of FIs including diabetes, burns, trauma, broad-spectrum antibiotic use, the use of immunosuppressive agents in transplant patients, cytotoxic chemotherapy use in patients with cancer, receiving care in an intensive care unit, the disruption of the innate immune system of surgical patients, and the use of catheters and other indwelling devices. In general, *Aspergillus*, *Cryptococcus*, and *Candida* are the major fungal pathogens responsible for invasive FIs (Table 1). There is a significant increase in infections caused by other emerging molds (including *Scedosp* bimetallic *orium* species, *Fusarium* species, and mucorales) and yeasts (including *Candida auris*). Although pathogenic fungi exert harmful effects, less importance has traditionally been given to FIs compared with other infections caused by parasites, viruses, and bacteria. Moreover, owing to concomitant public awareness, pathogenic fungi and FIs have recently been indicated as the neglected epidemic or hidden killers (Wall and Lopez-Ribot, 2020).

3. Currently available antifungal drugs and their limitations

The availability of a limited number of AFAs plays a significant role in the increased level of FI-associated mortality and morbidity. Similar to humans, fungi are a group of eukaryotic organisms. Unfortunately, there is a scarcity of selective targets that can be utilized to develop antifungal drugs. Therefore, the number of currently available antifungal drugs (Table 1) is markedly lower compared to antibacterials. The development of antifungal drugs has slowed down since the 1990 s. In addition, two decades have already passed since the newest class of AFAs (the echinocandins) reached the market. In general, four classes of Food and Drug Administration (FDA)-approved AFAs are currently available for clinical use to treat invasive FIs, namely, echinocandins, azoles, flucytosine, and polyenes (Wall and Lopez-Ribot, 2020). Nonetheless, unpleasant properties and side effects have greatly restricted their use. Azoles are the most commonly used AFA in clinical practice; however, the major problem lies in their interactions with drugs that are substrates of cytochrome p450 (CYP450) enzymes. These interactions can result in azole drug resistance and off-target toxicity (Mohd-Assaad et al., 2016). In terms of polyenes, they bind to fungal ergosterol, which is structurally similar to mammalian cholesterol. Therefore, AmB, a major polyene AFA, shows infusion-associated reactions and severe nephrotoxicity. Consequently, the dosage of AmB is highly regulated and it is typ-

ically substituted by one of the triazole antifungal drugs (voriconazole). Allylamines are usually utilized to treat superficial FIs including onychomycosis of the toenails or fingernails. In addition, 5-fluorocytosine (5-FC) is a highly effective AFA that is highly hepatoxic and can cause bone-marrow suppression. Furthermore, 5-FC monotherapy can induce marked fungal resistance. Combination therapy with 5-FC and AmB is used clinically to treat severe cases of cryptococcosis and candidiasis. A number of AFAs have been used as treatments for decades; however, the therapeutic outcomes of these AFAs are still unsatisfactory. These conventional AFAs show increased toxicity, and fungi usually develop resistance against them. They also present different efficacies in terms of oral bioavailability and tissue penetration.

Overall, voriconazole and 5-FC are small molecules that exhibit enhanced tissue penetration compared with larger amphipathic agents (including echinocandins and AmB) and more lipophilic agents (including itraconazole). In addition, echinocandins and AmB tend to accumulate in tissues and show delayed drug metabolism (Felton et al., 2014). Current improvement approaches include identifying novel fungal antigens to develop vaccine candidates, discovering novel targets for AFAs, and assessing other currently available drugs for their possible antifungal actions. The use of nanotechnology is another potential approach to encapsulate or modify currently available AFAs to enhance their effectiveness. So far, various nanomaterials have been studied and presented as innovative AFAs, such as biodegradable co-polymeric and polymeric-based structures including lipid-based nanosystems, metallic nanocomposites, and MNPs. Moreover, the size range of NPs offers them the capacity to transport currently available AFAs via several routes of administration including intraocular, nasal, and oral routes (Du et al., 2021).

4. Nanoparticles in drug delivery

The use of DDSs can enhance most of the pharmacological properties of conventional drugs including particulate carriers and their associated therapeutics. DDSs are designed in such a way that they can serve as drug reservoirs (for example, as sustained-release systems) and/or change the biodistribution and pharmacokinetics of their associated drugs. Indeed, new techniques are urgently needed to fight against resistant microorganisms in order to decrease the clinical burden. The development of nanotechnology-based antimicrobials might be an effective strategy, acting as antimicrobials as well as carriers (Makvandi et al., 2020). There is growing interest in nanotechnology that involves synthesizing NPs to ameliorate the physicochemical properties of materials for the benefit of humans (Chau et al., 2022). The advantages of NP-based delivery include its scalable production, safety assessment, and opportunity for clinical trials (Hagbani et al., 2022). The size of NPs ranges from 1 to 100 nm and they can be produced via top-down approaches including electro-explosion, sputtering, etching, laser ablation, and mechanical milling. In addition, NPs can also be prepared via bottom-up methods including reverse micelle methods, soft and hard templating methods, sol–gel methods, solvothermal and hydrothermal methods, and chemical vapour deposition (Baig et al., 2021). Nanoscale DDSs have gained popularity because of their exceptional capacity to allow the reaction to be attained effectively (Baig et al., 2021). A range of nanocarriers including dendrimers, polymersomes, carbon nanotubes, liposomes, and micellar nanocarriers have already been studied to identify effective drug carriers (N. Mody et al., 2014). Dendrimers can effectively deliver various drugs owing to their various unique properties including their convenient synthesis methods, available internal cavities, water solubility, polyvalency, higher level of branching, and nanoscale uniform size (Sherje et al., 2018).

Polymersomes contain amphiphilic block copolymers that have suitable properties as drug carriers, such as their capacity to encapsulate numerous drugs, surface functionality, long circulation time, tunable membrane permeability, and increased stability. Carbon nanotubes can also play roles as effective nano-containers for the delivery of various drugs. Carbon nanotubes are nanomaterials that also possess several unique features including their capacity to deliver drugs to targeted sites, high stability, exceptional electrical and optical features, higher level of drug loading capacity, flexible interaction with cargo, substantial strength, needle-like structure, and higher surface area (Zare et al., 2021). Liposomes are nanocarriers that have been found to be effective in targeted drug delivery. These nanocarriers are phospholipid vesicles composed of one or more concentric lipid bilayers that enclose distinct aqueous spaces. Liposomes have the unique capacity to entrap both hydrophilic and lipophilic compounds that enable many drugs to be encapsulated by phospholipid vesicles. Polymeric micelles are nanoscale drug-delivery systems consisting of amphiphilic block copolymers. The unique properties of polymeric micelles include good solubilization properties, easier sterilization and preparation methods, and smaller size; however, they have complicated characterization processes and lower stability in biological fluids (Ghezzi et al., 2021). On the other hand, MNPs are composed of a metal core consisting of inorganic metal or metal oxide that is typically covered with a shell composed of organic or inorganic material or metal oxide (Khan, 2020). Metal-based nanomaterials are continuously being evaluated for their applications because of their potential uses. MNPs have a higher surface area and show potential. Owing to these properties, MNPs have wide applications in various fields including drug delivery, medicine, food product, cosmetics, agriculture, paints, electronics, optics, and sensors (Hashem et al., 2022; Perveen et al., 2022).

5. Metallic nanoparticles and their antimicrobial properties

In medicine, there is growing interest regarding the applications of MNPs including gold (Au), platinum (Pt), silver (Ag), zinc (Zn), iron (Fe), copper (Cu), and many others. Various noble MNPs including Ag, Au, and Pt have been utilized for a number of biomedical applications including gene delivery and antifungal treatment (Fig. 1), diagnostic assays, antibacterial treatment, thermal ablation, drug delivery, radiotherapy enhancement, and anticancer therapy (Yaqoob et al., 2020). Furthermore, MNPs can be functionalized by several functional groups in order to target a diverse range of cells, along with potential biocompatible polymers including polyethylene glycol (Fan et al., 2018). Various classes of metal and metal oxide NPs have already exhibited antimicrobial functions including Au, magnesium oxide (MgO), copper oxide (CuO), silica (Si), calcium oxide (CaO), zinc oxide (ZnO), titanium dioxide (TiO_2), Ag, and Ag oxide (Ag_2O) (Dizaj et al., 2015; M. Hasanin et al., 2022a; Hashem et al., 2023). It has been observed that the antimicrobial effects of NPs rely on their intrinsic properties, surface modification, composition, and types of microorganisms. It has also been confirmed that the combined forms of NPs and antibiotics or antimicrobial peptides have shown enhanced antimicrobial effects at lower concentrations. The interactions between the metals and fungal cells are essential for homeostasis and fungal resistance (Robinson et al., 2021). Fungi can also be effectively used for the production of NPs with antimicrobial effects, owing to their capacity for mass production, their ability to be economically grown, and their increased levels of natural metal resistance (Jamdagni et al., 2018).

Ag is a transition metal that plays the role of a potent AFA for the elimination of microorganisms. In farm animals, Ag exerts positive effects on aflatoxins, intestinal microflora, and mycotoxin

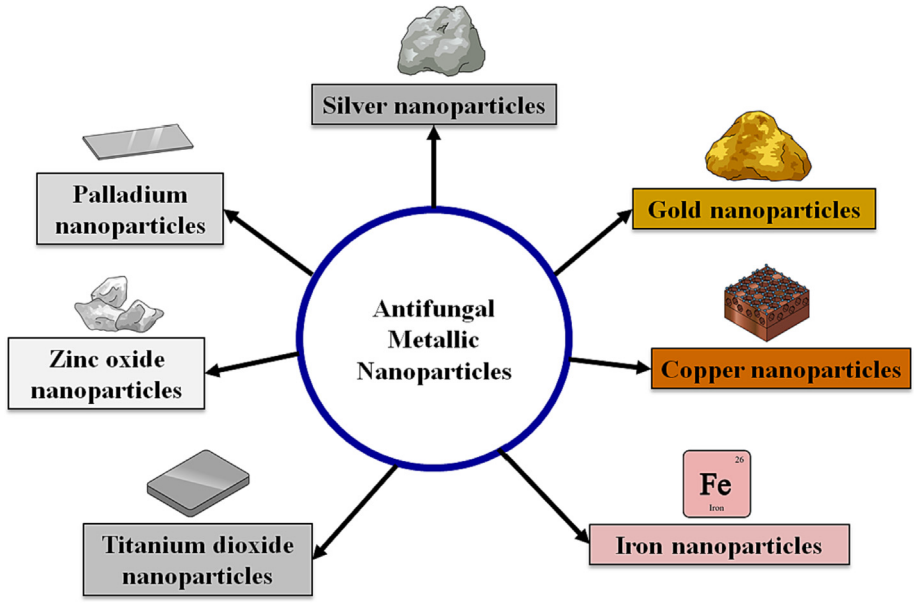

Fig. 1. Metallic nanoparticles that can play the role as antifungal agents.

absorption. In the food industry, Ag is also utilized in packaging owing to its antimicrobial effects (Gurunathan et al., 2022). Ag^+ shows a higher affinity for phosphate and sulfhydryl (thiol) groups in enzymes essential for the synthesis of cell walls in fungi and bacteria. Furthermore, Ag has the capacity to interfere with the energy production and electron transport chain. In addition, Ag^+ suppresses the respiratory chain and DNA replication in fungi and bacteria as well as eventually causing cell death via the production of reactive oxygen species (ROS). In general, AuNPs are non-toxic, bio-compatible, and safer compared with other inorganic NPs. The redox behavior of Au is useful in decreasing the concentrations of ROS generated during NPs exposure. It has been reported that AuNPs showed potential antimicrobial effects against several *Candida* clinical strains (de Alteriis et al., 2018).

Compared with other NPs in the same group of elements, ZnO NPs showed more potent antimicrobial effects against several types of microorganisms. ZnO NPs show high catalytic activity and strong ultraviolet (UV)-absorbing effects; therefore, these NPs are extensively utilized as effective UV blockers and in the preparation of cosmetic lotions (Gurunathan et al., 2022). Interestingly, ZnO NPs have been utilized to induce the degradation of water pollutants via photocatalytic function. These NPs also exerted increased cytotoxic effects via elevating the generation of ROS, which further results in oxidative damage and, ultimately, cell death. ZnO NPs showed marked suppressive properties on the growth of *Candida albicans* (*C. albicans*) by directly interacting with the fungal cell membrane and influencing its contact with the cell wall, which can further avert growth and result in cell death. NP exposure to fungal cells can decrease the level of oxidative enzymes and the efficiency of their anti-oxidative mechanisms, as well as disturbing their cellular integrity and osmotic balance (Gurunathan et al., 2022).

Cu is a biocompatible metal associated with several physiological mechanisms and it has been efficiently utilized to eliminate pathogens (Gurunathan et al., 2022). On the other hand, titanium dioxide (TiO_2) is an inorganic NP that is highly lipophilic, antibacterial, and non-toxic. This NP was found to mediate the decomposition of bacteria and provide protection from UV rays. Owing to these useful functions, TiO_2 is extensively utilized in consumer applications and industry. There are three forms of TiO_2 crystal structures: brookite, rutile, and anatase. TiO_2 NPs exerted strong antimicrobial effects against *C. albicans* in the absence or presence

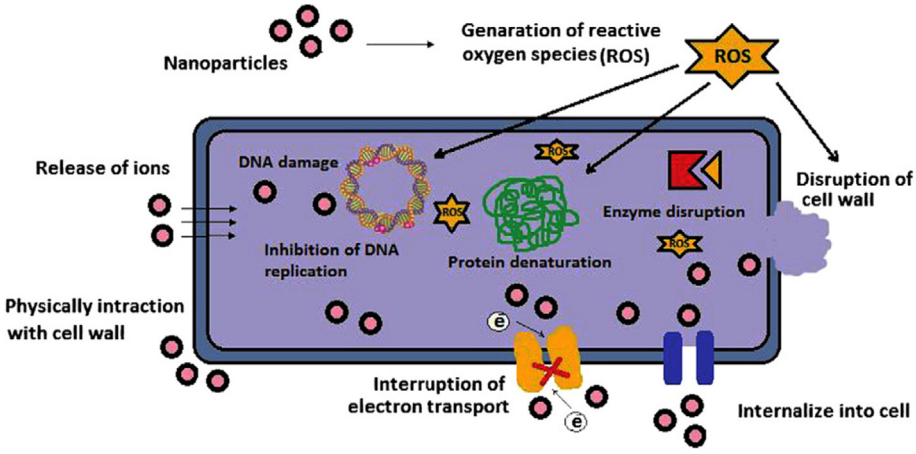

Fig. 2. Antimicrobial mechanisms of metallic nanoparticles. Reproduced with permission from Elsevier (Dizaj et al., 2014).

of sunlight. In general, iron oxide NPs (IONPs) are non-toxic and safe, and they are extensively utilized owing to their biochemical properties, magnetic properties, and lower cost in a range of medical applications. Furthermore, IONPs have broad-spectrum antifungal, bactericidal, antiparasitic, antiviral, antibiofilm, and wound-healing properties. There is growing interest in IONPs because of their significant physiochemical properties and they have been widely used in various applications including water treatment, catalysis, electronics, and biomedicine (Gurunathan et al., 2022). Antimicrobial mechanisms of various MNPs are illustrated in Fig. 2.

6. Metallic nanoparticles as a drug delivery system

MNPs have the capacity to elevate the therapeutic index of drugs via their site specificity, by averting multidrug resistance, and through the effective delivery of therapeutic agents (Beg et al., 2017; Rahman et al., 2020). MNPs are widely used as carriers in drug delivery for numerous therapeutic agents including peptides, chemotherapeutic drugs, nucleic acids, antibodies, and many others. The majority of the MNPs including Cu, Zn, titanium, palladium, Au, and Ag NPs have increased levels of tunable optical properties. In addition, their surfaces could be easily functionalized in order to conjugate active biomolecules and targeting agents via electrostatic interactions, covalent bonding, and hydrogen bonding. Several drugs can also be easily loaded to attain higher therapeutic efficacy. MNPs have the capacity to eliminate or inhibit fast renal drug excretion, increase the circulation time of drugs in the blood, and elevate the aqueous solubility of a hydrophobic drug compound. Compared with conventional NPs, multifunctional NPs possess a higher capacity to achieve multiple goals, including target-specific delivery via surface ligand decoration. The three major goals of drug delivery include controlled drug release to prevent the classical underdosing or overdosing cycle, reducing the adverse effects of the drug on healthy organs or tissues, and achieving site-specific drug delivery. In order to achieve all these goals, the coatings of MNP surfaces were improved to regulate the drug loading, delivery, and release in the target areas. The purposes of this surface coating included decreasing side effects, enhancing biocompatibility, and endowing the MNPs with the appropriate functional groups for better drug combinations (Chandrakala et al., 2022).

Effective drug delivery via MNPs relies on two major factors: the development of effective MNPs for prolonged and slow drug release, and the capacity of MNPs in site-specific drug delivery without affecting the other normal cells (Delcassian et al., 2019). These aforementioned factors could be easily achieved via passive and active targeting. MNPs have been widely explored in various studies for the diagnosis, detection, and treatment of multiple diseases. There is growing interest regarding MNPs owing to their exclusive size- and material-dependent physicochemical properties, which are nearly impossible to achieve with organic NPs. Clinical uses of various FDA-approved metal-NP–based nanomedicines were found to include exhibiting improved effectiveness and bioavailability of DDSs, along with decreasing the level of side effects due to their exclusive properties including active cellular uptakes or enhanced targeted delivery. It has been observed that by fine-tuning their shapes and sizes, doping methods, and surface chemistry, the developed MNPs can undergo rapid decomposition under certain physiological conditions and are therefore freely absorbed via multiple metabolic pathways without disturbing healthy tissues (Chandrakala et al., 2022). In Fig. 3, the potential applications of MNP-based delivery systems in delivering a range of substances are summarized.

7. Green synthesis and applications of metal-based nanomaterials

Green synthesis is essential to avert the production of dangerous or unwanted by-products via the use of eco-friendly, sustainable, and dependable synthesis techniques (Abu Hajleh et al., 2021; Chopra et al., 2022; Ghaderi et al., 2021; M. S. Hasanin et al., 2022). Three major factors that need to be considered in terms of green synthesis include the use of environmentally safe

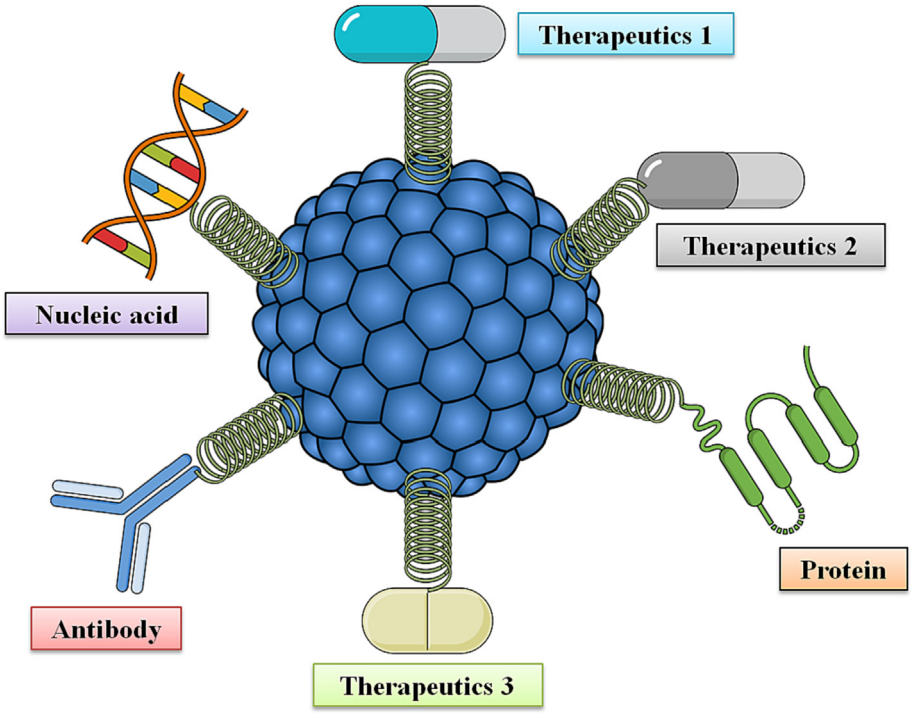

Fig. 3. Applications of the metallic-nanoparticle-based delivery system.

NP stabilizers, non-toxic reducing agents, and a suitable solvent medium. Green synthesis using plant extracts can be compared to some conventional methods. Mass generation of atomically precise MNPs needs highly reactive materials and/or energy consumption, which are not regarded as environmentally friendly. In order to overcome the aforementioned problems, researchers have started to utilize more environmentally benign approaches that are collectively known as green synthesis. Green synthesis of MNPs involves the use of a range of green technology or biological techniques along with the proper dimension and increased stability, as they are produced in a one-step synthesis. Therefore, the green synthesis of MNPs has embraced a range of biological materials including plants and plant products, bacteria, viruses, yeast, algae, and fungi. Many scientists even opt for green synthesis because of several advantages including the use of external investigational settings such as high pressure and high energy not being compulsory. This can further save energy and make the process environmentally friendly since toxic chemicals are not utilized, in addition to making the process cost-efficient since the biological component itself can act as both the capping and reducing agents. Numerous MNPs have been synthesized utilizing several plants as it is an easy and simple process to manufacture MNPs at a large scale, in comparison with bacterium- and/or fungus-mediated synthesis (Alarjani et al., 2022; Susanti et al., 2022; Ye et al., 2022).

The plant-mediated biosynthesis of MNPs is a ground-breaking approach that has several uses in the industries of food, agriculture, and medicine to enhance the lifespan of NPs (Ibrahim et al., 2021). This can take place because of the physicochemical properties of the plant-based MNPs that can also overcome the restriction of typical physical and chemical approaches of NP synthesis (Kalpana and Devi Rajeswari, 2018). Three different methods can be used in the plant-based green synthesis of MNPs including extracellularly (utilizing plant extracts), and intracellularly (inside the plant), by utilizing phytochemicals. Plants can mediate the intracellular generation of MNPs, since plants have the ability to accumulate metals and alter these intracellularly accumulated metals to NPs (Susanti et al., 2022). In the reduction of metals, a number of biomolecules including terpenoids, tannins, saponins, phenolics, ketones, flavones, aldehydes, alkaloids, vitamins, reducing sugars, carbohydrates, amino acids, and proteins in the plant are responsible for a significant contribution. In addition, these biomolecules have amine, carbonyl, and hydroxyl groups that can react with metal ions and reduce their particle sizes on a nanoscale. For instance, flavonoids possess multiple functional groups and the hydroxyl functional group of flavonoids is supposed to be accountable for the reduction of metal ions into NPs (Dikshit et al., 2021; Marslin et al., 2018). Furthermore, flavonoids have the capacity to mediate the bioreduction of the metal ion to the nanoscale and assist with capping NPs, which is crucial for biocompatibility and stability (Javed et al., 2020). In a single reaction, various reducing agents including alkaloids, sterols, and phenolics have the ability to reduce the metal ions into NPs (Susanti et al., 2022).

The nature and type of metal utilized for the biosynthesis of MNPs largely govern the NPs end-use industry. Various metals including Au, Cu, Ag, and many others have already been extensively utilized for the synthesis of NPs, utilizing various plant species or plant extracts (D. Zhang et al., 2020). Ag and Au were initially employed in the plant-extract-mediated synthesis of NPs. Numerous plants, including *Rhododedendron dauricam*, *Cassia auriculata*, *Ocimum* leaf, *Jatropha curcas*, *Nelumbo nucifera*, *Datura metel*, *Aloe barbadensis*, and *Acalypha indica*, have been used to generate Ag NPs. In addition, *Pelargonium graveolens* leaf, *Cinnamomum camphora*, *Diopyros kaki*, *Magnolia kobus*, *Medicago sativa*, and *Aloe barbadensis* Miller have been used to synthesize AuNPs (Jeevanandam et al., 2016). Furthermore, metals from their constituents have been stabilized and reduced using several phytonutrients and macromolecules including phenolic acids, terpenes, ethyl alcohols, flavonoids, phenolics, reducing sugars, and proteins (Susanti et al., 2022). MNP synthesis is typically started by mixing the plant extract or biomass with noble metal salt precursors with biomaterial at a preferred pH and temperature. The presence of several compounds of biomolecules can play a role as capping and reducing agents for the biosynthesis of NPs from their metal salt precursors. Initially, the reduction of metal salt precursors to their following NPs can be demonstrated by observing the alteration in the color of the colloidal solution (Sriramulu et al., 2020).

8. Metallic-nanoparticle-based antifungal therapeutic strategies

8.1. Gold nanoparticles (AuNPs)

AuNPs are extensively used in bionanotechnology owing to their multiple surface functionalities and unique properties. The simple functionalization of AuNPs offers a versatile platform for nanobiological assemblies with proteins, antibodies, and oligonucleotides. It has been demonstrated that AuNP bioconjugates are effective in the development of novel biomaterials for studying biological systems. Khan et al. (Khan et al., 2012) revealed that AuNP–methylene blue conjugates markedly decreased the formation of biofilms. Interestingly, the shape of NPs also affects their antimicrobial properties. NPs of different sizes including nanowires, nanospheres, and nanocubes were used to evaluate the effect of the shape of the AuNPs and AgNPs, and their effects were evaluated on several fungal species including *Candida tropicalis*, *Candida glabrata*, and *C. albicans*. In addition, it was observed that Au and Ag nanocubes showed greater antifungal effects against the test species compared with nanowires or nanospheres. In another study, Seong et al. (Seong and Lee, 2018) used the CaspACE FITC-VAD-FMK In Situ Marker to assess the activation of metacaspase. Compared with untreated cells (16.65%), they observed an elevated level of metacaspase activation in cells treated with H_2O_2 (51.87%), AuNPs (35.83%), and N-acetylcysteine-pretreated AuNPs (31.82%) (Fig. 4) (Seong and Lee, 2018). Furthermore, AuNPs also directly interacted with DNA and further resulted in DNA fragmentation and nuclear condensation. AuNPs have the capacity to disturb mitochondrial calcium homeostasis and also cause mitochondrial calcium overload. Therefore, the disturbance of mitochondrial calcium homeostasis induced AuNP-mediated cell death in *C. albicans* (Seong and Lee, 2018). It was also observed that AuNPs could markedly suppress dental pulp stem cell (DPSC) invasion and the formation of a pathogenic biofilm. In addition, treatment with AuNPs activated immune-response-associated genes in DPSCs, which further enhanced the functions of the host immune responses against pathogens.

Stabilized cationic dipeptide-capped Au/Ag nanohybrids were used to evaluate the antimicrobial properties, where peptide-capped AgNPs showed elevated antimicrobial properties compared with unconjugated MNPs, native peptides, or peptide-capped AuNPs. Tannic acid and sodium borohydride were used as reducing agents to prepare AuNPs. Subsequently, both were studied for their antifungal effects against *Saccharomyces cerevisiae* (a fungal pathogen) and *C. albicans*. It was observed that AgNPs exhibited stronger antifungal effects than AuNPs (Khatoon et al., 2018). On the other hand, compared with quercetin alone, quercetin-functionalized AuNPs exhibited a substantial antioxidant effect. In addition, it showed antifungal properties against *A. fumigatus* (a pathogenic filamentous fungus) at the concentration range of 0.1–0.5 mg/mL (Milanezi et al., 2019). Interestingly, heparin-functionalized AuNPs (AuHep-NPs) with a particle size of 530 nm exerted considerable antifungal properties against *Candida parapsilosis*, *Issatchenkia ori-*

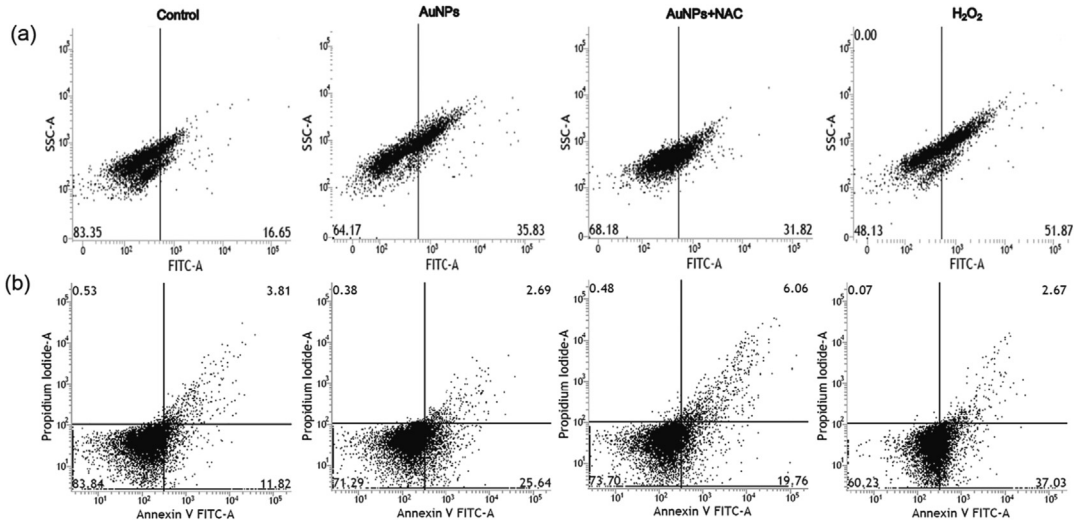

Fig. 4. Gold nanoparticles induced apoptosis (a) Activation of caspase in C. albicans as measured by FITC-VAD-FMK (a fluorescent analog of the pan-caspase inhibitor) assay and evaluated by flow cytometry, where the y-axis denotes the side scatter and x-axis denotes the FITC-VAD-FMK fluorescence. (b) Externalization of phosphatidylserine during early apoptosis evaluated by FITC-annexin V and PI double staining, and evaluated by flow cytometry, where the y-axis denotes the propidium iodide fluorescence and the x-axis shows the Annexin V FITC fluorescence. Reproduced with permission from Elsevier (Seong and Lee, 2018).

entalis (*Candida krusei*), and *C. albicans* (del Pilar Rodriguez-Torres et al., 2020; Gurunathan et al., 2022). Rahimi et al. (Rahimi et al., 2019) evaluated the anticandidal properties of indolicidin (a host defense peptide) and conjugated it with AuNPs against fluconazole (FCZ)-resistant *C. albicans* clinical isolates. These researchers used the biophysical properties to characterize the conjugation of indolicidin. They also evaluated the hemolytic and cytotoxic properties of the nanocomplex (Rahimi et al., 2019). Furthermore, the immunomodulatory properties of various peptide–nanomaterial conjugates and *ERG11* (the responsible gene for antifungal resistance) expression levels were also evaluated (Rahimi et al., 2019). The nanocomplex was found to be nontoxic for erythrocytes and fibroblast cells. In addition, nanocomplex treatment markedly decreased the expressions of *iNOS* gene in macrophages and the *ERG11* gene in FCZ-resistant *C. albicans* isolates (Rahimi et al., 2019).

In another study, Jebali et al. (Jebali et al., 2014) prepared, characterized, and assessed the antifungal properties of conjugated triangular AuNPs, peptide ligands, and triangular AuNPs against 30*C. albicans* clinical isolates obtained from individuals suffering from vaginal candidiasis. They reported that all conjugated triangular NPs and naked triangular AuNPs showed enhanced antifungal properties; however, this property was not observed with any peptide ligands. In another study, Gholami-Shabani et al. (Gholami-Shabani et al., 2016) developed a cell-free system to generate AuNPs by using purified sulfite oxidoreductase (a fungal oxidoreductase) of *Fusarium oxysporum* (*F. oxysporum*). These researchers used the disk diffusion method to assess the antifungal activities of prepared NPs. They observed strong growth inhibitory properties against all tested human pathogenic molds and yeasts, as demonstrated by inhibition zones ranging from 10 to 18 mm (Gholami-Shabani et al., 2016). Collectively, it was indicated that the preparation of NPs by using a purified sulfite oxidoreductase of *F. oxysporum* can be effective in producing safe bioactive AuNPs, which can be effectively used in the field of medicine (Gholami-Shabani et al., 2016). In Table 2, a summary of the antifungal potentials of various MNPs and metal oxide NPs has been provided.

8.2. Copper nanoparticles (CuNPs)

Cu is one of the promising candidates among nanometals to design a new generation of preparations. Cu is a nontoxic heavy metal and an important trace element. This metal plays role in numerous important metabolic processes. Cu showed substantial bactericidal and bacteriostatic properties by damaging proteins, nucleic acids, and cell membranes (Zangeneh et al., 2019). CuNPs showed significant antifungal properties against *Candida* species, antibacterial properties against a range of Gram-negative and Gram-positive bacteria, and antioxidant activities against various free radicals including 2,2-diphenyl-1-picrylhydrazyl (DPPH) without exerting any cytotoxic effects against human normal cells (Hemmati et al., 2020; Zangeneh et al., 2019). Several studies have already confirmed the antifungal property of CuNPs against several fungi. Various forms of Cu suppressed the growth of fungal hyphae in a dose-dependent manner (Oussou-Azo et al., 2020). It was observed that CuNPs exerted substantial suppressive properties against pathogenic fungi, and Cu was also found to trigger cell death via interacting with microorganisms. Cu caused denaturation of nucleic acids, protein alteration, membrane lipid peroxidation, and alteration of cell membrane permeabilization, which eventually resulted in cell death. Furthermore, copper's surface coatings showed antifungal properties (Arendsen et al., 2019).

The in vitro functions of Cu nanowires and CuNPs against *C. albicans* strains and yeast have been assessed (Martínez et al., 2021). It was revealed by microscopic analysis that treatment with Cu nanowires and CuNPs affected the cell walls and cell structure, which further resulted in a complete breakdown of the yeast. Cu nanowires and CuNPs showed noteworthy antifungal properties against *C. albicans* via inducing the release of free Cu^{2+} ions that played a role as a biocide. It was observed that the sharp edges of marigold-petal-like nanostructures damaged cell membranes and cell walls, and caused cell death in yeast. The sodium alginate- and starch-mediated preparation of CuNPs led to the generation of NPs that exhibited antifungal properties against *C. krusei* (a predominant nosocomial fungal pathogen) and *C. albicans* (Akturk et al., 2019). Copper oxide nanoparticles (CuO NPs) exhibited substantial antifungal and antibacterial properties against human clinical pathogens via the production of free radicals, specifically, nitric oxide radicals (Hashem et al., 2023; Mani et al., 2021; Saied et al., 2023). Spherical CuO NPs were prepared by utilizing black and green tea leaf extracts containing phenols and flavonoids, and particle sizes of 26–40 nm showed antifungal and antibacterial properties (Asghar et al., 2018). In addition, spherical CuO NPs were prepared by using seed extracts of *Persea americana* containing carboxylic acid alkanes with an average particle size of 42–90 nm.

Table 2
A summary of the antifungal potentials of various metallic nanoparticles and metal oxide nanoparticles.

Nanoparticles	Tested Fungal strains	References
Gold nanoparticles	Candida tropicalis, Candida albicans, Candida glabrata, Candida parapsilosis, Issatchenkia orientalis (Candida krusei), *Fusarium oxysporum*	(del Pilar Rodriguez-Torres et al., 2020; Gholami-Shabani et al., 2016; Gurunathan et al., 2022)
Copper nanoparticles	Cladosporium herbarum, C. albicans	(Akturk et al., 2019; Henam et al., 2019; Padmavathi et al., 2020)
Silver nanoparticles	C. tropicalis, C. albicans, *Malassezia furfur,* Cryptococcus species, Penicillium griseofulvum, C. krusei, Trichophyton mentagrophytes, C. parapsilosis, C. glabrata, Monilia albicans, Stachybotrys chartarum, Mortierella alpina, Chaetomium globosum, A. fumigatus, Cladosporium cladosporioides, Penicillium brevicompactum, Trichophyton rubrum, C. tropicalis, Aspergillus species, Fusarium species, F. oxysporum, Aspergillus awamori	(El Sayed and El-Sayed, 2020; Gurunathan et al., 2022; Gutiérrez et al., 2018; Mussin et al., 2019; Shih et al., 2019)
Iron nanoparticles	Mucor piriformis, Aspergillus niger, *Candida parapsilosis*, C. albicans, Penicillium chrysogenum, *Candida tropicalis, Candida glabrata* species, Alternaria alternata, C. herbarum, Trichothecium roseum	(De Lima et al., 2020; Devi et al., 2019; Gurunathan et al., 2022; Salari et al., 2018; Seddighi et al., 2017)
Zinc oxide nanoparticles	C. albicans, A. niger, Penicillium expansum, *Fusarium solani*, A. fumigatus, Fusarium graminearum	(Khan et al., 2021)
Titanium dioxide nanoparticles	C. albicans	(Moradpoor et al., 2021)
Palladium nanoparticles	Fusarium oxysporum, Colletotrichum gloeosporioides	(Osonga et al., 2020)

Indeed, these NPs exhibited antioxidant, antifungal, and antibacterial properties (Asghar et al., 2018). Microwave-mediated CuO NP preparation led to spherical CuO NPs with a particle size of 7–10 nm and these NPs exhibited antifungal properties against a common fungus *Cladosporium herbarum* (Fig. 5) (Henam et al., 2019). Furthermore, CuO NPs markedly triggered cell death in *C. albicans* by causing membrane damage and inducing ROS generation. This further resulted in the inhibition of the switch between yeast and hyphal growth by upregulating the negative regulator *tup1* and downregulating *ras1*, *hst7,* and *cph1* (Padmavathi et al., 2020).

8.3. Silver nanoparticles (AgNPs)

AgNPs are widely used in the industries of medicine, food, microelectronics, aerospace, and pharmaceuticals because of their unique physical, chemical, and biological intrinsic characteristics (Khojasteh-Taheri et al., 2023; Torabian et al., 2022). It has already been confirmed that AgNPs can be effectively used as drug carriers, antifungals, anticancer agents, antiviral agents, antiparasitic, antibacterial agents, biosensors, coatings for medical devices, and in bio-imaging (Hosseini Bafghi et al., 2021; Salleh et al., 2020). AgNPs have been shown to be effective tools in therapeutics (Patra et al., 2018), as they exhibit good traceability and penetration in the organism, exhibit adjustable surface functionalization and surface chemistry, require simple preparation, and have a high surface/volume ratio (Gomes et al., 2021). Mallmann et al. (Mallmann et al., 2015) prepared AgNPs by using sodium dodecyl sulfate as a stabilizer and ribose as a reducing agent. These researchers also evaluated the antifungal property of AgNPs against the common *Candida* species including *C. tropicalis* and *C. albicans*. It was observed that the stable NPs with a mean size of 12.5 ± 4.9 nm (mean ± SD) exhibited significant antifungal properties against *Candida* species (Mallmann et al., 2015).

Mussin et al. (Mussin et al., 2019) evaluated the in vitro suppressive effect of AgNPs against 41 clinical isolates of *Malassezia furfur* (a type of fungus). They also visualized the interaction between AgNPs and *Malassezia*, produced an antimicrobial gel of AgNPs–ketoconazole (KTZ), and assessed the combination with KTZ. Subsequently, the developed AgNPs were randomly dispersed around the surfaces of yeasts and exerted a fungicidal property with low minimum inhibitory concentrations (MICs). AgNPs did not exhibit any antagonistic activity against KTZ. The potent antifungal property of AgNPs and their accumulation in affected regions with an extended-release profile contributed to the substantial antifungal property of KTZ against *Malassezia* infections and various other superficial mycoses. Moreover, a carbopol-based gel was prepared with AgNP–KTZ in order to prevent recurrence, decrease the frequency of application, and ameliorate the topical therapy of superficial malasseziosis (Mussin et al., 2019). Xia et al. (Xia et al., 2016) assessed the antifungal activities of AgNPs against *Trichosporon asahii* (a pathogenic fungus). It was observed that AgNPs exhibited a potent suppressive activity on the growth of *T. asahii*. Interestingly, the MIC of AgNPs against *T. asahii* was 0.5 μg/mL, which was found to be higher than voriconazole and lower than itraconazole, FCZ, terbinafine, caspofungin, 5-flucytosine, and AmB. Moreover, AgNPs exerted strong antifungal

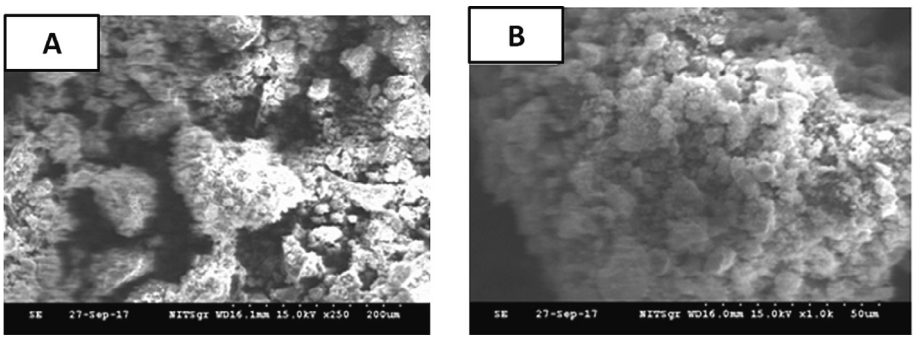

Fig. 5. Scanning electron microscope images of copper oxide nanoparticles (A and B). Reproduced with permission from Elsevier (Henam et al., 2019).

activity against *T. asahii* by penetrating the fungal cell as well as damaging various cellular components including the ribosome, chromatin, mitochondria, cell membrane, and cell wall (Xia et al., 2016).

The fungus *Arthroderma fulvum* (strain HT77) was utilized to biologically prepare AgNPs. The prepared NPs showed antifungal properties against several pathogenic fungi including *Fusarium*, *Aspergillus*, and *Candida* species. Furthermore, Pd@Ag nanosheets (Pd@Ag NSs) showed strong antifungal properties against common invasive pathogenic fungi including *Cryptococcus neoformans* (a fungal pathogen) complexes. It was observed that the anticryptococcal property of Pd@Ag NSs was markedly higher compared with FCZ and similar to AmB. In addition, Pd@Ag NSs showed fungicidal properties against *Cryptococcus* species by disturbing the energy metabolism, intracellular protein synthesis, and cell integrity. AgNPs also showed strong antifungal properties against *Candida* by producing ROS. These NPs also affected ergosterol content, as well as the altered cellular structure and membrane fluidity (Radhakrishnan et al., 2018). AgNPs derived from an extract of aqueous pigeon droppings suppressed a range of microorganisms, including *Bacillus* species, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. It was observed that AgNPs exhibited the lowest antifungal property against *Penicillium griseofulvum* (a fungal pathogen responsible for infection of the toenails and fingernails) and the highest antifungal property against the pathogenic fungus *Aspergillus flavus (A. flavus)* (Gurunathan et al., 2022). Das et al. (Das et al., 2016). observed that the coating of the surfaces of biogenic AgNPs with ZnO elevated its antimicrobial property against the fungal pathogen *C. krusei*. Propolis-extract-mediated AgNPs (Pro-AgNPs) showed antifungal properties against a range of fungal species, such as *Trichophyton* sp., *Microsporum* sp., *Fusarium* sp., and *Candida* sp. In combination with FCZ, AgNPs suppressed the growth of FCZ-resistant *C. albicans* via elevating endogenous ROS generation and abrogating drug efflux pumps. AgNP treatment reduced membrane fluidity and membrane ergosterol concentrations as well as downregulated CDR2, ERG25, ERG11, and ERG1. AgNPs also decreased the membrane contents of Cdr2p and Cdr1p, and therefore, efflux pump activities. Interestingly, a combination of ZnO-, metallic-, Au-, and Ag-NPs efficiently regulated the growth of four strains of mycotoxin-producing molds including *A. fumigatus* and *A. flavus*. AgNP treatment also markedly suppressed the growth of six fungal species, including as *Trichophyton mentagrophytes*, *C. krusei*, *C. parapsilosis*, *C. glabrata*, and *C. albicans* via suppressing the normal budding process and modifying the cell membrane structure (J. Kim et al., 2009).

It was reported that AgNPs immobilized on chitosan (CS) improved its antifungal properties against *Monilia albicans* (Shih et al., 2019). Moreover, a nanocomposite comprising AgNPs and pullulan (a polysaccharide polymer) showed antifungal properties against *Aspergillus niger*. It has also been confirmed that AgNPs can play a role as AFAs; however, their antifungal potential was found to be dependent on their zeta potentials, shapes, and sizes. Indeed, the suppression mechanism of fungi was found to vary with particle sizes. AgNPs showed strong antifungal properties against several pathogenic fungi, such as *Stachybotrys chartarum*, *Mortierella alpina*, *Chaetomium globosum*, *A. fumigatus*, *Cladosporium cladosporioides*, *Penicillium brevicompactum*, *Trichophyton rubrum*, *C. tropicalis*, and *C. albicans*. The effects of AgNPs were evaluated against several pathogenic fungi that result in fungal keratitis (a sight-threatening disease). In addition, AgNPs showed antifungal properties with MICs of 0.5, 0.5, and 1 μg/mL for *Alternaria alternata*, *Aspergillus* species, and *Fusarium* species, respectively. The use of elevated concentrations of Ag-embedded mesoporous silica NPs (mSiO2@AgNPs) by utilizing leaf extracts of *Azadirachta indica* (neem) showed strong antifungal properties against *C. albicans*. It was observed that AgNPs functionalized with phenolic compounds exhibited potent antifungal properties against *A. niger* by disrupting mycelial growth and spore germination. Ultrasmall Ag nanoclusters (rsAg@NCs) were biologically prepared by utilizing metabolites from usnioid lichens and showed significant antimicrobial properties against FCZ-resistant *C. albicans*, which was found to be markedly greater than FCZ and chemically prepared AgNPs. The rsAg@NCs triggered apoptosis by the production of ROS, which further resulted in metacaspase activation, chromosomal condensation, DNA fragmentation, and loss of the mitochondrial membrane potential (Prateeksha et al., 2020).

Synthesized AgNPs via *Mucor hiemalis* exerted substantial antibacterial properties against three pathogenic fungi (including *A. flavus*, *Fusarium oxysporum*, and *C. albicans*) and six pathogenic bacteria (including *S. aureus*, *Bacillus cereus*, *E. coli, Aeromonas hydrophila, Pseudomonas brassicacearum,* and *Klebsiella pneumonia*). AgNPs in combination with various antibiotics (including rifampicin, kanamycin, tetracycline, and streptomycin) suppressed bacterial growth. Moreover, AgNPs in combination with various fungicides (including KTZ, FCZ, and AmB) suppressed the growth of fungi. Synthesized AgNPs, using an aqueous extract of *Eucalyptus camaldulensis*, exhibited potent fungicidal properties by disrupting the adhesion and invasion of *Candida* into host cells by decreasing the release of a hydrolytic enzyme and the formation of germ tube. AgNPs also downregulated the expressions of various genes including *ZAP1*, *TEC1*, *EFG1*, *ECE1*, *HWP1*, and *ALS3* that encode proteins essential for the development of the biofilm and hyphal growth. Moreover, AgNPs downregulated SAP4, LIP9, and PLB2, which encode various hydrolytic enzymes (Wunnoo et al., 2021). Biosynthesized AgNPs utilizing the fruit extract of *Cinnamomum camphora* showed significant antifungal properties against the fungal pathogen *F. oxysporum* by suppressing conidia germination and colony growth (D. Zhang et al., 2020). MNPs prepared by using *Fusarium solani* exhibited substantial antifungal properties against multidrug-resistant (MDR) strains of *S. aureus* and *P. aeruginosa* along with their mycotoxigenic effects against *F. oxysporum*, *A. fumigatus,* and *Aspergillus awamori* (El Sayed and El-Sayed, 2020).

Kamli et al. (Kamli et al., 2022) showed that combinations of noble and transition metals can exert synergistic antimicrobial actions. They biosynthesized Ag-Ni NPs by utilizing an aqueous leaf extract of *Salvia officinalis*. The antifungal properties of Ag-Ni NPs alone and in combination with FCZ were evaluated against FCZ-resistant *C. albicans* isolates. In addition, they also assessed the effects of these NPs on the formation of biofilms, drug efflux pumps, and membrane integrity. The minimum fungicidal concentration (MFC) (3.12 μg/mL) and MIC (1.56 μg/mL) values suggested strong antifungal properties of Ag-Ni NPs against FCZ-resistant *C. albicans*. Following the combination, synergistic interaction was seen between FCZ and Ag-Ni NPs against *C. albicans* 5112 along with a fractional inhibitory concentration index value of 0.31. At higher concentrations (3.12 μg/mL), Ag-Ni NPs disrupted the integrity of the membrane and exerted anti-biofilm effects. However, the morphological transition was stopped at a lower concentration (0.78 μg/mL). Furthermore, Ag-Ni NPs also blocked the efflux pumps in the FCZ-resistant *C. albicans* 5112. It has been observed that the targeting of efflux pumps and biofilms by novel drugs can be an effective technique in fighting against MDR strains of *C. albicans*. Collectively, these findings suggest the use of Ag-Ni NPs to prevent infections triggered by drug-resistant *C. albicans* strains (Kamli et al., 2022).

8.4. Palladium nanoparticles (Pd NPs)

Pd NPs have various unique properties, including optical properties, electronic properties, and chemical and thermal stabilities. These NPs can also be biofunctionalized to enable their medical uses (Bharathiraja et al., 2018; Zhou et al., 2018). Pd NPs have been

used as prodrug activators, drug carriers, and photothermal agents. There is an increasing interest in their cytotoxic, antioxidant, and antimicrobial effects. There are several methods that can be used to synthesize Pd NPs including electrochemical and chemical precipitation, chemical reduction, and the sol–gel method. Nonetheless, there is growing interest in green chemistry for the synthesis of Pd NPs by using biocompatible and eco-friendly products including various microorganisms (including yeast, fungi, viruses, and bacteria) and seaweeds (Fahmy et al., 2020; Puja and Kumar, 2019). Osonga et al. (Osonga et al., 2020) synthesized PdNPs by using environmentally friendly and low-cost techniques at ambient temperatures. Quercetin diphosphate (QDP) is a naturally derived flavonoid, which is used as a stabilizing, capping, and reducing agent. The optimum temperature was used to synthesize perfectly spherical Pd NPs with average sizes ranging from 0.1 to 0.3 μm in diameter. Considerably smaller particles were synthesized with an average size distribution of 1–7 nm at a comparatively higher QDP concentration. The researchers confirmed the formation of NPs by using several characterization techniques including X-ray diffraction, energy-dispersive X-ray spectroscopy, transmission electron microscopy (TEM), and UV–Vis spectroscopy. High-resolution TEM was also used to confirm the lattice structure of PdNPs. The prepared PdNPs were tested for their antifungal activities against *Fusarium oxysporum* and *Colletotrichum gloeosporioides*. It was observed that the particle sizes of PdNPs have a significant contribution to their antifungal properties (Osonga et al., 2020).

8.5. Iron oxide nanoparticles (IONPs)

IONPs usually contain a magnetic iron oxide (maghemite, γ-Fe_2O_3 or magnetite, Fe_3O_4) core. These NPs can be prepared via numerous chemical approaches and enclosed by a coating for their stabilization (Dadfar et al., 2019; Geppert and Himly, 2021). In terms of biomedical applications, there is growing interest in IONPs because of their non-toxicity, biocompatibility, and superparamagnetic properties. In addition, IONPs can also be effectively used as gene and drug carriers for target-specific gene therapy and drug delivery, respectively. Moreover, the surface coating of IONPs elevated their stability, reduced their cytotoxicity, and enhanced antimicrobial property of IONPs (Abbas and Krishnan, 2020). IONPs were prepared by using *Platanus orientalis*, and these NPs exerted marked antifungal properties against *Mucor piriformis* compared with *A. niger* (Devi et al., 2019). Salari et al. (Salari et al., 2018) assessed the capacity of biofilm formation of several strains of *Candida* and compared the antibiofilm properties of Fe_3O_4-NPs with FCZ. Fe_3O_4-NPs at various concentrations effectively decreased the biofilm formation in *Candida parapsilosis* and *C. albicans* compared with FCZ. Fe_2O_3-NPs with average particle sizes of 10–30 nm were prepared by using tannic acid as a capping and reducing agent. Subsequently, the effects of the synthesized NPs were assessed utilizing *A. niger*, *A. alternata, Penicillium chrysogenum, C. herbarum,* and *Trichothecium roseum*. Among various fungal species, Fe_2O_3-NPs showed potent antifungal activities against *A. niger* and *P. chrysogenum*. Interestingly, FCZ on CS-coated IONPs effectively suppressed *Candida* planktonic cells (De Lima et al., 2020; Gurunathan et al., 2022).

In another study, Seddighi et al. (Seddighi et al., 2017) assessed the potential of IONPs against FIs caused by *Candida* species. These researchers characterized IONPs using a vibrating sample magnetometer, Fourier transform infrared spectroscopy, X-ray diffraction, and scanning electron microscopy. They also assessed and compared the antifungal properties of IONPs against different *Candida* species with FCZ. The synthesized IONPs were spherical and had an average particle size of 30–40 nm. In addition, the MFC and MIC values of IONPs were found to range from 500 to 1000 μg/ml and 62.5 to 500 μg/ml, respectively. In contrast, the MFC and MIC values ranged from 64 to 512 μg/ml and 16 to 128 μg/ml, respectively. It was observed from the growth suppression values that IONPs showed potent antifungal properties against *Candida glabrata* species, *Candida albicans*, and *Candida tropicalis*. IONPs also showed antifungal activities against *Candida* species and suppressed the growth of all the evaluated *Candida* species. However, more in vivo and in vitro studies are essential to evaluate whether IONPs can be effectively used for medicinal purposes (Seddighi et al., 2017). Zare-Khafri et al. (Zare-Khafri et al., 2020) evaluated the antifungal potentials of magnetic IONPs against FCZ-resistant colonizing isolates of *C. albicans* and also estimated the *ERG11* gene expression and ergosterol content. They observed that 93% of C. albicans isolates were resistant to FCZ (Zare-Khafri et al., 2020). Interestingly, magnetic IONPs showed effects against FCZ-resistant colonizing isolates of *C. albicans* with MICs at 250–500 μg/ml. In addition, the ERG11 gene expression was found to be downregulated in FCZ-resistant colonizing isolates of C. albicans. Furthermore, the ergosterol content was also found to be decreased (Zare-Khafri et al., 2020).

8.6. Zinc oxide nanoparticles (ZnO NPs)

ZnO NPs are metal oxide NPs with a particle size of less than 100 nm. There are three major method types that can be used to synthesize ZnO NPs including physical, biological, and chemical methods. In addition, chemical synthesis can be further divided into gas phase synthesis and liquid phase synthesis. Chemical methods involve emulsion and micro-emulsion methods, hydrothermal methods, solvo-thermal methods, the sol–gel method, precipitation in the presence of a surfactant, a precipitation process, and mechanochemical processes. Chemical methods were found to be the most environmentally friendly, reliable, and cost-effective. Furthermore, they offer flexibility for the modification of the shape and size of synthesized NPs (Bisht and Rayamajhi, 2016). At similar FCZ concentrations, ZnO NPs coated with CS–linoleic acid suppressed the growth of FCZ-resistant clinical strains. ZnO NPs suppressed C. *albicans* in a concentration-dependent manner. At the MIC of 0.1 mg/mL, ZnO NPs suppressed *C. albicans* growth by over 95%. The loss in viability of *C. albicans* was decreased in the presence of histidine, which indicates the role of ROS (including singlet oxygen and hydroxyl radicals) in cell death. It was revealed that nano-ZnO doped with 5% nano-Pd, micro-ZnO, and pure nano-ZnO exerted antifungal effects against *A. niger* with MICs of 1.25, 5 and 2.5 mg/mL, respectively. Among them, nano-ZnO markedly induced cell death in *Aspergillus* compared with their non-nano counterparts (Gondal et al., 2012). He et al. (He et al., 2011) revealed that treatment with ZnO NPs (12 mmol l^{-1}) for 12 days completely suppressed the germination of *P. expansum* conidia, and the conidial development of *P. expansum* was inhibited (Fig. 6C and D) (He et al., 2011). Collectively, these findings indicate that ZnO NPs altered and damaged *P. expansum* conidia, which ultimately resulted in significant inhibition of fungal growth (He et al., 2011).

In a dose-dependent manner, ZnO NPs surrounded by a mesoporous nanosilica ($mSiO_2$) matrix (ZnO@$mSiO_2$) suppressed the growth of four fungal strains. It was observed that ZnO NPs significantly decreased the formation of germ tubes in *C. albicans* by reducing the release of proteinase and phospholipase. ZnO NPs also penetrated the cell and severely damaged the cell membrane and cell wall (Jalal et al., 2018). ZnO NPs functionalized with gallic acid exerted antifungal properties against several types of fungal strains, such as *Fusarium solani*, *A. fumigatus*, and *C. albicans* (Khan et al., 2021). ZnO quantum dots dose- and time-dependently suppressed radial growth against two fungal species: *C. albicans* and *A. fumigatus*. Cierech et al. (Cierech et al., 2016)

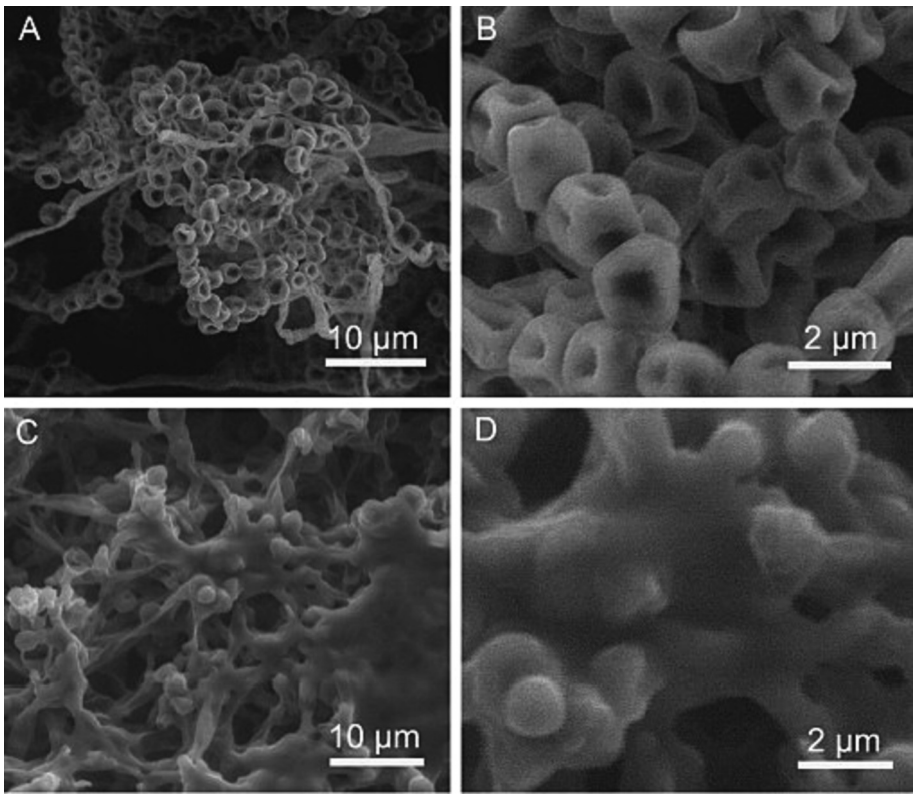

Fig. 6. Scanning electron microscopy images of Penicillium expansum before (A and B) or after (C and D) treatment with zinc oxide nanoparticles. Reproduced with permission from Elsevier (He et al., 2011).

revealed that in a concentration-dependent manner, doped ZnO NPs and poly (methyl methacrylate) showed antifungal effects by the suppression of biofilm deposition on the surface. In addition, in a dose-dependent manner, the biosynthesis of ZnO NPs from *Syzygium aromaticum* (SaZnO NPs) decreased the growth and generation of zearalenone and deoxynivalenol in *Fusarium graminearum* via ROS accumulation. Treatment with SaZnO NPs exerted harmful effects on the integrity of the fungal membrane, depleted ergosterol content, and enhanced lipid peroxidation (Lakshmeesha et al., 2019).

8.7. Titanium dioxide nanoparticles (TiO2 NPs)

Titanium (Ti) is one of the most abundant metals found in the earth's crust. In nature, Ti is not found in the metallic state. In addition, $^{+}4$ is the most common oxidation state of Ti, but $^{+}2$ and $^{+}3$ also exist. In industry, metallic Ti, $TiCl_4$, and TiO_2 are extensively used. Indeed, TiO_2 NPs are widely used in medicine and industry, such as in water purification and DDSs. TiO_2 NPs also have exclusive antimicrobial, photocatalytic, electronic, and optical properties (Fig. 7) (Rajakumar et al., 2012). In the rutile and anatase forms, TiO_2 NPs showed substantial antifungal properties against *C. albicans*, and the loss of cell viability was time- and dose-dependent. Furthermore, TiO_2 NPs also altered the cell structure (Ahmad et al., 2019). Photocatalytic paints formulated with the anatase TiO_2 NPs showed antifungal properties against *A. niger* via their high photocatalytic function. The antifungal property of photocatalytic paints has been confirmed by utilizing *A. niger* (Zacarías et al., 2018). Moradpoor et al. (Moradpoor et al., 2021) revealed that TiO_2 NPs showed substantial antifungal properties against oral *C. albicans*. Under visible light, F and N co-doped TiO_2 NPs with average particle sizes of 200–300 nm were utilized as AFAs. Moreover, the colloidal form allowed the effective interaction of the NPs with the cell walls of the fungi, and visible light-mediated production of ROS by the NPs led to the destruction of the fungus (Gurunathan et al., 2022; Mukherjee et al., 2020).

The antifungal properties of ZnO and TiO_2 NPs were compared with AmB against several *Candida* species. It was observed that ZnO and TiO_2 NPs showed antifungal properties against pathogenic *Candida* species. However, their antifungal properties were markedly lower than those of AmB (Kermani et al., 2021). In a study by Ilkhechi et al. (Najibi Ilkhechi et al., 2021), the sol–gel method was used to develop several metal oxide NPs including ZnO–TiO_2, TiO_2, and ZnO, and these developed NPs (50 μg/mL) inhibited fungal growth. Interestingly, the antifungal property of ZnO–TiO_2 against *A. flavus* was much higher than ZnO and TiO_2. Furthermore, TiO_2 and ZnO-TiO_2 (300 μg/ml) suppressed 100% of spur generation. Both TiO_2 and ZnO exhibited spherical and pyramidal shapes. On the surface, ZnO-TiO_2 nanopowders showed both pyramidal and spherical shapes with grown particles (Najibi Ilkhechi et al., 2021). At the concentration of 150 μg/ml, ZnO-TiO_2 exerted an antifungal effect by inducing oxidative stress and elevating the level of ROS generation, compared with ZnO and TiO_2 (Najibi Ilkhechi et al., 2021). Collectively, the aforementioned findings suggest that ZnO–TiO_2 NPs can be effectively used as an AFA (Najibi Ilkhechi et al., 2021). However, more studies are required to reveal the comprehensive antifungal mechanism of these NPs. It has been observed that UV-irradiated TiO_2 NPs can cause cell damage by attacking microbial phospholipids (Gurunathan et al., 2022). TiO_2 triggered the generation of ROS by directly interacting with the bacterial membranes. Moreover, microbial cell membranes possess a negative charge, while TiO_2 NPs possess a positive charge on their surface, which further increases their interaction (Gurunathan et al., 2022).

TiO_2 NPs exhibit a higher affinity towards membrane proteins and can cause alteration of their structures. It was demonstrated that photocatalysis can affect the capacity of TiO_2 NPs to bind with phospholipids and phosphoproteins (Gurunathan et al., 2022).

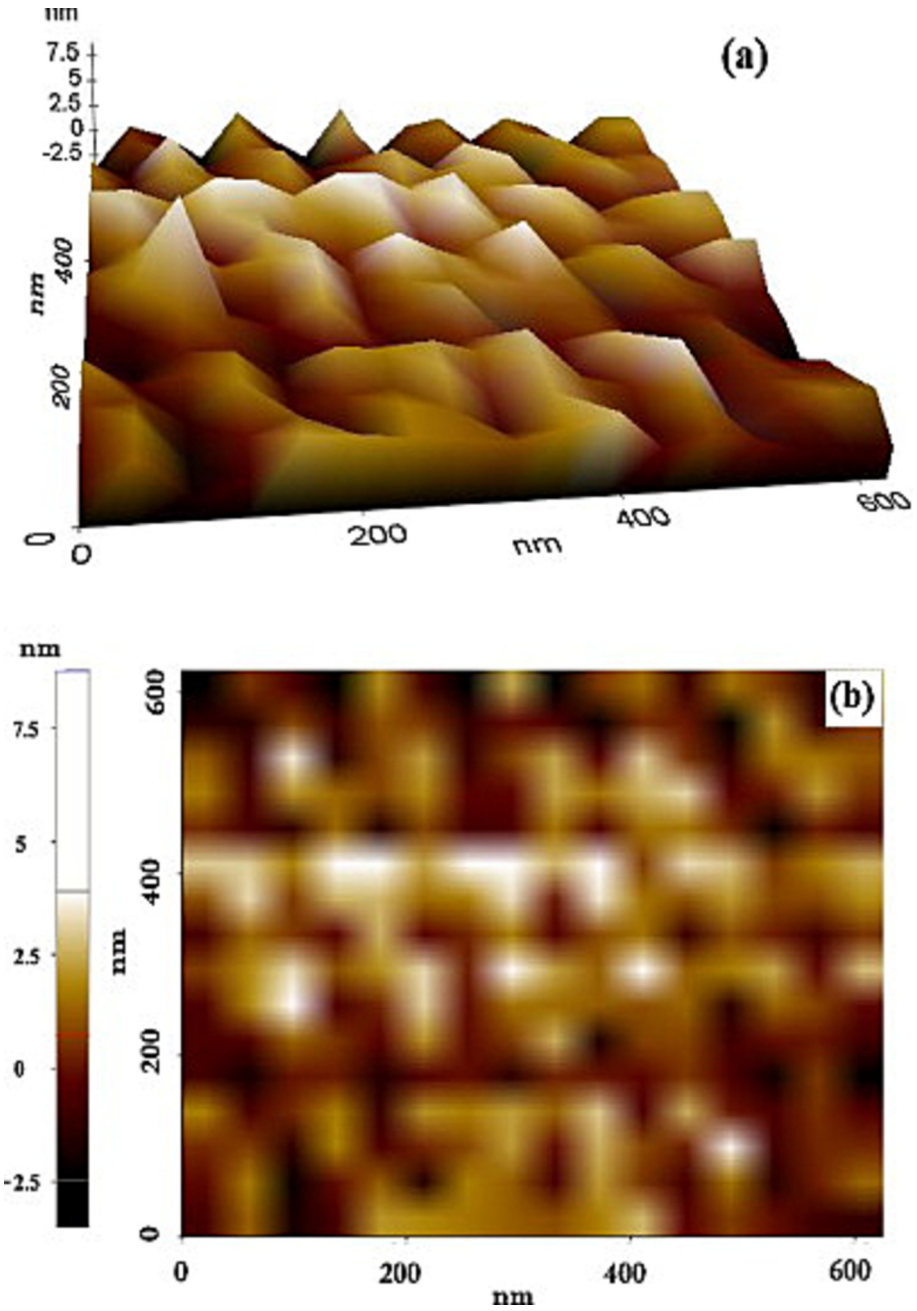

Fig. 7. Atomic force microscope images of synthesized titanium dioxide particles. (a) cross-sectional view, and (b) top view. Reproduced with permission from Elsevier (Rajakumar et al., 2012).

Under UV light, the electron-holes in nano-TiO_2 were found to react with oxygen and water to produce ROS (particularly hydroxyl radicals) to achieve antimicrobial activity (Korshed et al., 2018). CS NPs adversely affected the cell membrane activities and exerted antibacterial effects. Elevating the CS concentration elevated chitin degradation, which resulted in the destruction of the cell walls of the pathogens and eventually led to antifungal effects (Gurunathan et al., 2022; Xing et al., 2021). Treatment with nano-TiO_2 generated strong oxides including hydroxyl radicals, which further destroyed the permeable barrier, disrupted the cell wall membrane, damaged cell components, and destroyed the unsaturated bonds in organic molecules, which eventually resulted in cell death (Gurunathan et al., 2022).

9. Toxicity of metal nanoparticles

Despite the many advantages of MNPs as antifungal agents and drug delivery systems, their toxicological properties also require consideration. The toxicity of MNPs is reliant on various physicochemical properties; therefore, different MNPs have specific toxicity mechanisms due to their specific properties, and the extent of their toxicities also varies accordingly (Attarilar et al., 2020). As an AFA, the dose of AgNPs needs to remain sufficiently low so as to not cause human cell cytotoxicity (Attarilar et al., 2020). Moreover, the toxic effects of AgNPs have been found to be closely linked to their concentrations. The toxicity of AgNPs was also found to be reliant on numerous factors, such as their chemical

and physical properties (Z. Guo et al., 2018). Along with their particle size, the genotoxicity and cytotoxicity of AgNPs are linked to their exposure time, concentration, surface oxidation to form silver oxides, particle aggregation, coating, etc. (Akter et al., 2018; Attarilar et al., 2020). Prolonged exposure to ZnO NPs can lead to various unwanted effects owing to their ability to reach any organ or tissue (Medici et al., 2021). It has been reported by various in vivo and in vitro studies that ZnO NPs can exert various molecular effects including cell apoptosis activation, reduction in cellular viability, and loss of membrane integrity. ZnO NPs-associated cytotoxicity was found to be size- and shape-dependent; for example, spherical nanoparticles of approximately 40 nm showed greater toxicity compared with larger nanospheres. Interestingly, nanorods showed greater toxicity compared with spherical ZnO NPs. In addition, the surface composition of ZnO NPs was also found to be linked to their toxic effects.

Several in vitro and in vivo studies have been carried out to explore the genotoxicity and cytotoxicity potential of TiO_2 NPs. Nonetheless, various conflicting results have been observed in these studies. Little to no toxic effects have been observed in some studies, while others have observed that TiO_2 NPs can exert oxidative, genotoxic, and cytotoxic effects through oxidant generation, inflammation, and apoptosis. TiO_2 NPs also interfered with cell metabolism, damaged DNA, caused oxidative stress, and mediated ROS generation. Intravenous administration of 35 nm TiO_2 NPs caused pregnancy complications in pregnant mouse models (Yamashita et al., 2011). Consequently, more studies are required to fully reveal the toxicological profile of TiO_2 NPs (Ziental et al., 2020). Conflicting findings have been observed in terms of the toxicity of AuNPs. Various studies have confirmed that the effects of AuNPs are particle-size-dependent. The particle size of AuNPs largely determines the effectiveness of endocytosis, which is an important mechanism closely associated with the accumulation and localization of NPs inside the cell (Lopez-Chaves et al., 2018). It was reported that 1.4 nm AuNPs were found to exhibit the most cytotoxicity, whereas slightly larger AuNPs were three to five times less toxic, and bigger AuNPs (up to 15 nm) did not exhibit toxicity. However, in a different study, it was reported that 45 nm AuNPs were associated with higher toxicity than smaller AuNPs. Wu et al. (L. Wu et al., 2022) showed that ultrasmall IONPs with diameters of 4.2 and 2.3 nm exhibited higher toxicity and were found to be lethal at a dose of 100 mg/kg (L. Wu et al., 2022). However, they did not observe any toxic effects with 9.3 nm IONPs (L. Wu et al., 2022).

10. Possible directions for further research

Indeed, it is very difficult to meet the current clinical requirement owing to the growing occurrence of antifungal resistance and the limited number of available AFAs. Azole, echinomycin, and polyene are commonly used AFAs. The current development of novel AFAs mainly focuses on structural modification to enhance their safety and efficacy; however, additional efforts are required to identify new targets and develop NP-based AFAs. Notwithstanding the tremendous understanding regarding the future prospect of NPs and nano-DDSs, their actual impact on the healthcare system including antifungal drug delivery remains very limited. Several studies have already shown the potential of MNPs as AFAs; however, more studies are required with their hybrids. Furthermore, more studies are required to reveal their detailed antifungal mechanisms (Xu et al., 2021). The relevant toxic effects of MNPs also need to be evaluated using unbiased and internationally agreed in vivo toxicological models. The design, validation, and adaptation of such models need to be carefully considered for toxicity studies, the sterility of NPs, the coating material, and the route of exposure.

11. Conclusion

Conventionally, antimicrobial agents should contain high efficiency, a broad spectrum, and sustained antimicrobial properties. In addition, these agents should have excellent biocompatibility and stability. NPs have a great future as AFAs owing to their exclusive antimicrobial properties. In general, MNPs have wide applications in biomedical science. Owing to their excellent antifungal activity, they can be effectively used as an alternative to traditional AFAs to overcome antifungal resistance. Since the mechanisms of action of MNPs differ from those of conventional AFAs, they are likely to be effective against fungal pathogens that have already developed antifungal resistance. In addition, MNPs can exert their antifungal effects against fungal pathogens by targeting several biomolecules, which compromises the development of resistant strains. On the other hand, any potential risk of adverse or toxic events when using metal nanoparticles in humans is linked to their route of administration, dosage, and physicochemical properties. MNPs typically have a narrow therapeutic window; therefore, extensive physicochemical characterization is required during the early stages of therapeutics development. Extensive in vivo studies are also needed during preclinical and clinical studies for successful pharmaceutical development to avert any failures in the late phases of drug development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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