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Title:
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Date:
2023-03-01

Citation:
Huang, T., Li, X., Maier, M., O'Brien-Simpson, N. M., Heath, D. E. & O'Connor, A. J. (2023). Using inorganic nanoparticles to fight fungal infections in the antimicrobial resistant era. Acta Biomaterialia, 158, pp.56-79. https://doi.org/10.1016/j.actbio.2023.01.019.

Persistent Link:
https://hdl.handle.net/11343/339575

Acta Biomaterialia 158 (2023) 56–79

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actbio

Review article

Using inorganic nanoparticles to fight fungal infections in the antimicrobial resistant era

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ARTICLE INFO

Article history:
Received 28 September 2022
Revised 20 December 2022
Accepted 6 January 2023
Available online 11 January 2023

Keywords:
Antifungal
Antimycotic
Toxicity
Antimicrobial mechanisms
Nanoparticle fabrication

ABSTRACT

Fungal infections pose a serious threat to human health and livelihoods. The number and variety of clinically approved antifungal drugs is very limited, and the emergence and rapid spread of resistance to these drugs means the impact of fungal infections will increase in the future unless alternatives are found. Despite the significance and major challenges associated with fungal infections, this topic receives significantly less attention than bacterial infections. A major challenge in the development of fungi-specific drugs is that both fungi and mammalian cells are eukaryotic and have significant overlap in their cellular machinery. This lack of fungi-specific drug targets makes human cells vulnerable to toxic side effects from many antifungal agents. Furthermore, antifungal drug resistance necessitates higher doses of the drugs, leading to significant human toxicity. There is an urgent need for new antifungal agents, specifically those that can limit the emergence of new resistant species. Non-drug nanomaterials have primarily been explored as antibacterial agents in recent years; however, they are also a promising source of new antifungal candidates. Thus, this article reviews current research on the use of inorganic nanoparticles as antifungal agents. We also highlight challenges facing antifungal nanoparticles and discuss possible future research opportunities in this field.

Statement of significance

Fungal infections pose a growing threat to human health and livelihood. The rapid spread of resistance to current antifungal drugs has led to an urgent need to develop alternative antifungals. Nanoparticles have many properties that could make them useful antimycotic agents. To the authors' knowledge, there is no published review so far that has comprehensively summarized the current development status of antifungal inorganic nanomaterials, so we decided to fill this gap. In this review, we discussed the state-of-the-art research on antifungal inorganic nanoparticles including metal, metal oxide, transition-metal dichalcogenides, and inorganic non-metallic particle systems. Future directions for the design of inorganic nanoparticles with higher antifungal efficacy and lower toxicity are described as a guide for further development in this important area.

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https://doi.org/10.1016/j.actbio.2023.01.019

1. Introduction

Fungal infections threaten multiple aspects of human livelihood including health [1] and food supply [2]. Focusing on human health, fungi can cause life-threatening infections (mycosis), poisoning through the production of toxins (e.g., botulism), and allergic reactions to fungal proteins [3]. Fungal infections can be caused by endogenous, opportunistic species and exogenous pathogenic species [1]. Individuals with underdeveloped, suppressed, or weakened immune systems such as newborns, cancer patients receiving chemotherapy, organ transplant patients, burns patients, and patients with acquired immune deficiency syndrome (AIDs) are more susceptible to invasive fungal infections [3].

The rate of invasive fungal infections has increased significantly in recent decades. In fact, more than 1 billion people suffer from fungal infections annually, resulting in 1.6 million deaths globally [4,5]. Approximately 90% of fungal-related deaths are due to four fungal genera: *Candida* spp., *Aspergillus* spp., *Pneumocystis* spp. and *Cryptococcus* spp. [6]. More detailed introduction of these pathogenic fungal species and the diseases they could cause can be found in the literature [7,8]. Invasive fungal infections caused by *Candida* spp. and *Aspergillus* spp. in particular have high mortality rates of 30-50% [6]. *Candida* spp. are also of particular concern because they are responsible for up to 40% of the total mortality from all fungal infections [9]. Additionally, superficial infections in patients are commonly associated with pathogens such as *Trichophyton* spp., *Epidermophyton* spp. and *Microsporum* spp. [10]. Therefore, effective control of infections caused by these fungi is important for human health. The emergence of antimicrobial resistance worldwide is challenging human health. Naturally occurring opportunistic fungal pathogens have developed resistance to a wide range of antifungals [11]. To avoid a global collapse in our ability to control fungal infections, we must improve the management of existing antifungals, promote the discovery of new antifungals, and use emerging technologies to find alternative solutions.

Nanoparticles are small particles with size ranging from 1 to 100 nm [12]. Due to their small size and high surface area to volume ratio, nanoparticles possess many unique physiochemical properties that are significantly different from bulk materials. Based on these properties, nanoparticles have a wide range of applications, such as in cosmetics, clothing materials, building materials, agriculture, energy, catalysis, and medicine. Growing interest in the field of nanomedicine research has attracted significant attention. The main applications of nanoparticles in medicine include imaging, diagnostics, drug delivery, anti-cancer, and antibacterial treatments. The many compositions and forms of these particles make specific, minimally invasive diagnostics and treatments possible. Notably, nanoparticles can be modified to have different physiochemical properties, such as stability, size, shape, and surface charge, which can affect the biocompatibility and diagnostic or therapeutic functions of the nanoparticles. An overview of nanoparticles for medical applications can be found in Ref. [13].

Fighting against microbes is always an important task to protect human health. Nanoparticles with antibacterial abilities have become a hot topic over recent decades, as the challenge of antibiotic resistance has grown. These nanoparticles can help to overcome the limitations of traditional organic antibacterial drugs with regards to safety, broad-spectrum activity, and combating resistance, and have been applied in medical products like wound dressings.

2. Basics of fungal biology

It is crucial to understand fungal biology to develop more effective treatment and prevention methods for fungal infections. Fungal pathogens can be divided into two major groups: filamentous fungi and yeasts [14]. Most of the primary pathogens are filamentous fungi, while most of the opportunistic pathogens (which cause infections when a patient's immune defences are compromised) are yeasts [14]. The basic biology of filamentous fungi and their lifecycle is shown in Fig. 1(a) [15]. Filamentous fungi are generally composed of elongated, branched hyphae with cell walls, and typically reproduce sexually or asexually by producing a multitude of spores (as shown in Fig. 1(a)) [15]. Their hyphae are multicellular, filamentous, branching structures, comprising apically growing series of colourless cellular compartments separated by cell walls, as shown in Fig. 1(b) [16]. The structures of the hyphae are unique and are not found in other kingdoms of multicellular life such as plants and animals [17]. Each fungus grows a vast number of hy-

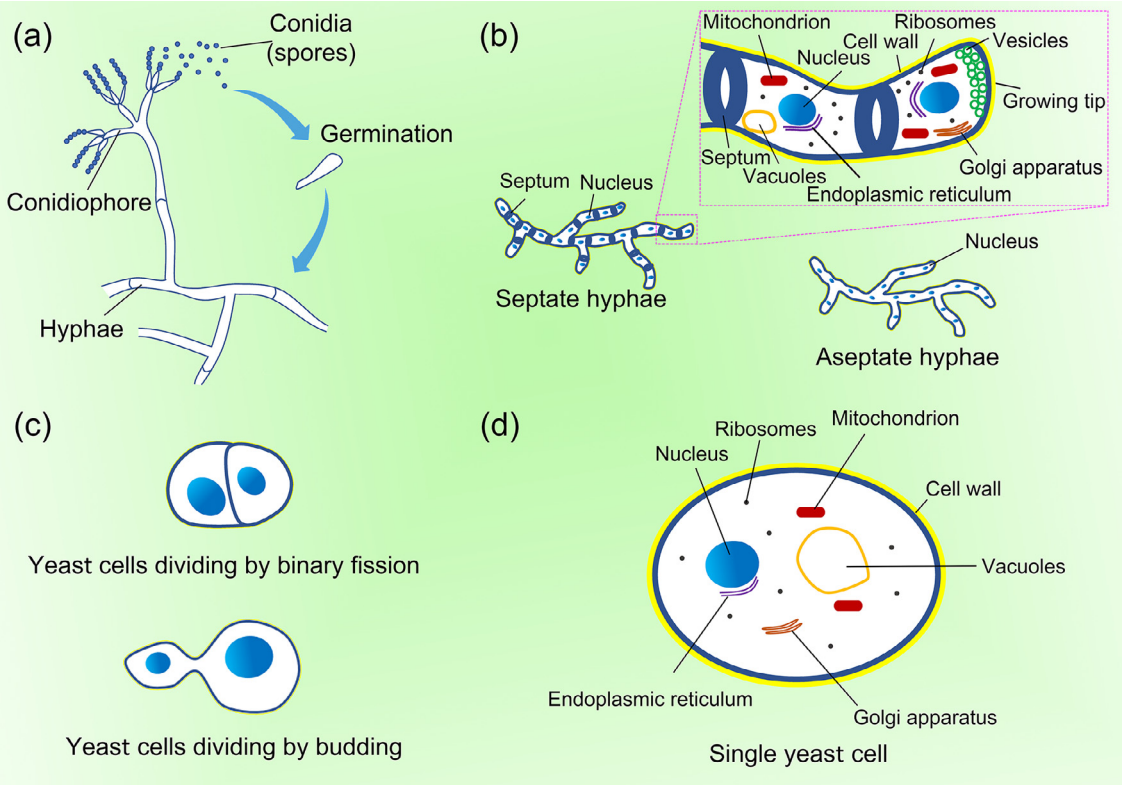

Fig. 1. (a) Representative structures and life cycle of fungi; (b) septate branched hyphae and aseptate branched hyphae; (c) schematic of yeast cells dividing by binary fission or by budding; (d) schematic of a single yeast cell.

phae that are intertwined into a tangled web called mycelium [16]. In contrast, yeasts grow as discrete cells. Some of them proliferate via fission, but proliferation by budding is more common as depicted in Fig. 1(c) [18].

Both mammalian cells and fungal cells are eukaryotic. As such, there is a significant similarity in their cellular structures as seen in Fig. 1(b, d). For instance, the plasma membrane of both cell types is a phospholipid bilayer, and fungi share many common organelles with mammalian cells, including a nucleus, ribosomes, Golgi apparatus, mitochondria, and endoplasmic reticulum. However, fungal cells do have some distinct cytoplasmic organelles and biosynthetic pathways that directly relate to their unique structural and functional characteristics [19]. For instance, the double-layered wall structure that encases fungal cells, known as the fungal envelope, has an inner plasma membrane and an outer cell wall [20]. Fungal cells differ from mammalian cells in that they possess an outer cell wall that is commonly composed of glycoproteins and polysaccharides, mainly glucan and chitin [20]. One main role of the fungal envelope is to provide protection for the fungal cells from environmental stresses, and it is also the site for a variety of signalling pathways [20]. Although both mammalian and fungal cells have cell membranes, their lipid compositions differ. Mammalian cells have a cholesterol-rich membrane, whereas fungal cells have a membrane composed mainly of ergosterol. Ergosterol is a molecule that serves a similar role in fungal cells as cholesterol does in mammalian cell membranes and is critical for the function and biogenesis of the membrane [21]. Ergosterol can be recognised as a fungi-specific target for designing antifungals that differ fungal cells from mammalian cells. Despite these differences, fungi are metabolically similar to mammalian cells with few pathogen-specific targets. More detailed descriptions of fungal structures and fungal classifications can be found in books, such as those by Webster *et al* [15,16].

3. Current antifungal drugs and challenges

3.1. Current antifungal drugs

The overlap in cellular machinery between fungi and mammalian cells hinders the development of antifungal drugs that only target fungi, without causing additional undesirable side effects for the mammalian cells [6]. Compared with antibiotics, the number of antifungal agents is small, and many antifungal drugs are toxic to eukaryotic host cells [22]. Ideas and techniques that have been effective for the development of antibacterial drugs have not shown similar efficacy upon translation to the development of antifungal drugs, as bacteria and fungi have critically different structures and components [23].

At present, approximately 80 types of antifungal drugs are clinically available. They can be categorised into five classes, including polyenes (such as amphotericin B), allylamines, azoles (such as fluconazole, itraconazole, posaconazole), pyrimidine analogues, and echinocandins (such as caspofungin, micafungin and anidulafungin) [6]. The antifungal mechanisms of these drugs can be further divided into four common targeting techniques, which are outlined in Table 1. The first common target for antifungal drugs is ergosterol [24]. Ergosterol is required for the function and biogenesis of the plasma membrane, and inhibiting its synthesis, binding to it, or damaging it can be lethal to fungi [25,26]. Other common targets for antifungal drugs include the cell envelope (both membrane-active and cell wall-active drugs are effective here) [27]; inhibiting the biosynthesis of nucleic acids, proteins, chitin, and mannan [27]; and other mechanisms, such as producing reactive oxygen species (ROS) or depleting adenosine triphosphate (ATP) [28,29]. Sulphur metabolism has been recently reported as a potential new antifungal target as sulphur-related processes are a fundamental aspect of the fungal physiology of some species, such as *Aspergillus fumigatus*

Table 1
Antifungal mechanisms of current antifungal drugs.

Category of antifungal mechanisms	Antifungal mechanism	Representative drugs	Refs.
Targeting ergosterol	Perturbing membrane function through binding to ergosterol	Amphotericin B	[14,31]
	Inhibiting ergosterol biosynthesis	Imidazoles, triazoles, allylamines and morpholines	[31]
Targeting the cell envelope	Disrupting membrane via pore formation	Antimicrobial peptides	[32]
	Inhibiting synthesis of fungal cell wall polysaccharides	Triazoles and echinocandins	[31]
Targeting biosynthesis	Inhibiting fungal protein synthesis	Sordarins	[31]
	Interfere with microtubule assembly	Griseofulvin	[31]
	Inhibits DNA synthesis	Flucytosine	[31]
	Inhibiting expression of mRNAs	Hinokitiol	[33]
	Inhibiting glycolysis	Benoate	[29]
Other mechanisms	Promoting ROS production	Amphotericin B, Dill seed essential oil	[28,34,35]
	Depleting ATP	Benoate	[29]
	Inhibiting the respiratory electron transport system	Pyrrolnitrin	[36]

[30]. However, no antifungal drug that targets sulphur metabolism has been reported so far.

Because yeasts and filamentous fungi differ in structure and composition, some antifungal mechanisms may be effective against only one or the other. For example, flucytosine exerts its antifungal activity by incorporating into RNA and causing premature chain termination or by inhibiting DNA synthesis. However, for this to occur, it must be internalized into the cell and converted to its active form through the activity of two enzymes. Most filamentous fungi lack these enzymes, so the antifungal activity of flucytosine is limited to yeasts [31]. As another example, the allylamines inhibit squalene epoxidase, which is involved in an early step in the ergosterol biosynthesis pathway in susceptible species, which include many filamentous fungi but few pathogenic yeasts [31].

3.2. Current antifungal challenges

Current antifungal drugs aid in the management of fungal infections; however, many challenges remain. Specifically, many antifungal drugs exhibit toxicity, and fungi are increasingly developing resistance [31]. The rise of antifungal resistance is particularly concerning, as this will limit the efficacy of future treatments, as is occurring for antibacterial drugs. The number of reports of drug-resistant human pathogenic fungi has increased rapidly over the past decades [11]. Drug resistance to common antifungal agents has greatly increased the difficulty of treating fungal infections clinically [37]. The global spread of azole-resistant *Aspergillus* spp. and rise of multidrug-resistant *Candida* spp. are particularly concerning due to the high mortality associated with invasive infections caused by these species [38,39]. Azoles are not only used for the health protection of human, animal and crop, but also used for antifouling coatings and wood preservatives. The widespread use of azole has accelerated the evolution of azole-resistant fungi [11]. In one surveillance study, the rates of resistant *Candida* spp. increased from 4.2% in 2008 to 7.8% in 2014 [40], and some institutional studies have reported higher rates of 10% or more [41–43]. For instance, the prevalence of fluconazole-resistant *Candida albicans* infections in The Ninth People's Hospital of Chongqing in China increased dramatically from 36% to 64% in only two years [43].

Fungi have developed several resistance mechanisms including alterations in drug targets, alteration in cellular pathways (such as alteration in sterol biosynthesis), reduction in the intercellular concentration of target enzyme, overexpression of the antifungal drug target, activation of stress response signalling, and overexpression of efflux pump proteins (Fig. 2) [44,45]. Besides, fungi have their intrinsic resistance mechanisms to antifungal drugs, including biofilm formation, differences in cellular permeability, and some mechanisms overlapping with those implicated in acquired resistance including target incompatibility, stress response signalling, and efflux pump proteins overexpression (Fig. 2).

Biofilms are communal structures of microorganisms encased in an extracellular polymeric matrix composed mainly of polysaccharides, lipids, proteins, external DNA (eDNA), and other molecules [46,47]. The composition of the extracellular polymeric substance varies across species and even growth conditions, and the composition of many biofilms remains unknown [48,49]. Biofilms can form on both biotic and abiotic surfaces, and are known to often attach to medical devices, such as urinary and intravenous catheters, artificial heart valves, endotracheal tubes, and prothesis joints [50]. Biofilms provide microorganisms protection against external factors such as temperature and pH variations, and can evade immune defences and impart antimicrobial resistance [50,51]. The National Institutes of Health reported that more than 80% of human infections are associated with biofilm formation [52]. In the United States, biofilm-related infections affect more than 12 million people with an estimated annual economic burden of 6 billion dollars [50]. Both yeast and filamentous fungi can form biofilms. The most common sites of fungal biofilm infections include mouth, lungs, burn wounds, lower genital tract, gastrointestinal tract, skin, intravascular and catheter insertion sites [47]. Among fungal pathogens, *Candida albicans* are most commonly associated with biofilm infections and induce high mortality [51]. Frequently, biofilms contain mixed populations of bacteria and fungi, which make the treatment much more difficult [53]. The limited number of antifungal agents, significant toxicity of these agents towards mammalian cells, the emergence of resistant species, and the protection provided by biofilms towards traditional antimycotic agents clearly illustrate the need to develop new antifungal agents to effectively treat and control resistant fungal infections [54].

4. Antifungal inorganic nanoparticles

Nanoparticles are promising next generation antimicrobial agents [55]. Their antibacterial properties have been extensively studied, but their use as antifungal agents has received less attention [56]. However, nanoparticles have many properties that could make them useful antimycotic agents. For instance, nanoparticles are highly tuneable, they have high specific surface area, and their unique physical and chemical properties allow them to attack microorganisms via several different mechanisms [57]. Our group and others have recently illustrated that attacking bacteria with nanoparticles that exert several simultaneous mechanisms of action can be an effective strategy to prevent or significantly delay the onset of antibacterial resistance [58,59]. Investigating whether this strategy could also limit fungal resistance development is a promising line of inquiry. Additionally, nanoparticles have been shown to penetrate biofilms and inhibit biofilm formation, so they

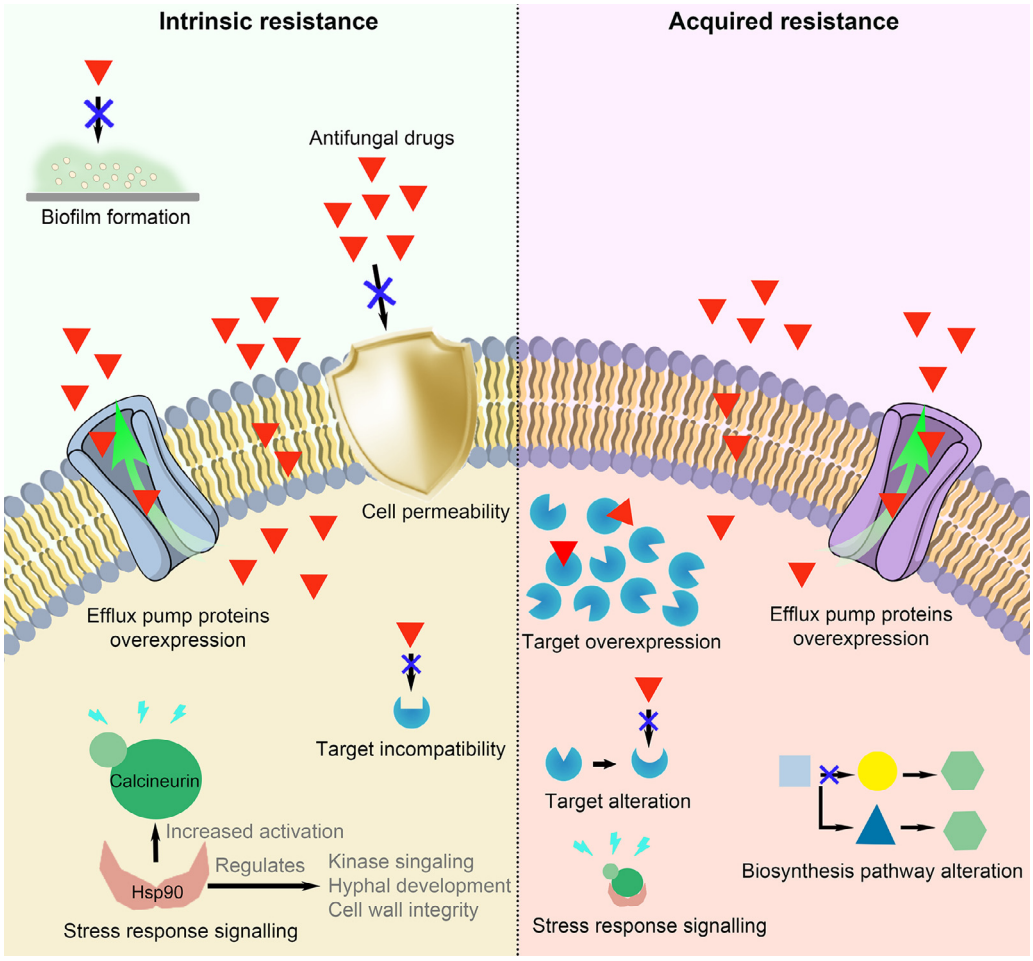

Fig. 2. The mechanisms of fungal acquired and intrinsic resistance which can be developed through several mechanisms. Examples include overexpression of drug targets, target alteration by amino acid replacements, signalling through stress response pathways, overexpression of efflux pump proteins, or alterations in cellular pathways. Intrinsic resistance includes several mechanisms overlapping with those described in acquired resistance, such as target incompatibility, stress response signalling, and efflux pump overexpression. Besides, intrinsic resistance can be caused by the formation of fungal biofilms and differences in cellular permeability. Created using Mind the Graph.

are a promising tool to prevent or treat fungal biofilm infections [60].

Both organic and inorganic nanoparticles with antimycotic properties have been developed, and each type of nanoparticle has unique benefits and limitations. In this review, we focus on inorganic nanoparticles because they have superior chemical and thermal stability compared to their organic counterparts, making them more easily stored, transported, and used in challenging environments [56]. We first discuss the existing research on antifungal inorganic nanoparticles including metal (silver, gold, and copper), metal oxide (zinc oxide, titanium dioxide, iron oxide, and copper oxide), transition-metal dichalcogenide (molybdenum disulphide and molybdenum diselenide), and inorganic non-metallic (carbon, selenium and tellurium) particle systems [61–68]. Their toxicity limitations and what is currently known about their mechanisms of action are reviewed to provide important insights into their potential applications. The antifungal NPs reviewed here are mostly made by chemical reduction or biosynthesis methods, as described in Section 8. Once existing research has been analysed, future directions for this technology regarding the design of inorganic nanoparticles with higher antifungal efficacy and lower toxicity are discussed.

4.1. Silver nanoparticles

Silver nanoparticles (Ag NPs) are the most widely researched inorganic nanoparticles for antimicrobial applications, including as antifungal agents [69]. They show broad-spectrum activity against bacteria and have been applied as antibacterial agents in a range of commercial products, including in wound dressings and as coatings on medical devices [70]. Ag NPs have also been found to have antifungal activity against a wide range of species, including *Aspergillus brasiliensis* [61], *Aspergillus fumigatus* [61], *Aspergillus oryzae* [71], *Bipolaris sorokiniana* [72], *Candida albicans* [73], *Candida auris* [74], *Candida glabrata* [75], *Chaetomium globosum* [76], *Cladosporium cladosporioides* [76], *Cryptococcus* sp. [75], *Magnaporthe grisea* [72], *Mortierella alpine* [76], *Penicillium brevicompactum* [76], *Penicillium chrysogenum* [71], *Rhizoctonia solani* [77], and *Stachybotrys chartarum* [76]. Importantly, this antifungal activity has also been demonstrated against drug-resistant fungal species [78]. Table 2 summarizes available data on their performance in terms of the minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) of the Ag NPs against different fungal strains. It must be noted that these studies used Ag NPs with different sizes and different stabilizer coatings, both of which can significantly affect their interactions with cells. The mean sizes of most Ag NPs mentioned in this table were very small, less than 25 nm. In only a few cases, Ag NPs prepared using biological extracts as reducing agents were larger, up to 80nm [79]. The reports also used a variety of MIC or MFC testing methods and different fungal sources. Thus, the resulting MIC and MFC values vary over a very wide range and the data from different reports are very difficult to compare. Therefore, this table provides a general guide of the antifungal ability of silver particles against different

Table 2
Minimum inhibitory concentrations (MIC) and minimum fungicidal concentrations (MFC) of Ag NPs against a variety of fungal strains.

Fungal strains	MIC (μg/mL)	Refs.	MFC (μg/mL)	Refs.
Aspergillus brasiliensis	/	/	1960	[80]
Aspergillus flavus	0.5-2	[81,82]	/	/
Aspergillus fumigatus	1	[81,82]	/	/
Aspergillus niger	25-64	[83,84]	/	/
Candida albicans	0.052-60	[79,81–93]	1.8-500	[80,86–90]
Candida auris	50	[74]	100	[74]
Candida dubliniensis	3.9-7.8	[86]	15.6-31.2	[86]
Candida glabrata	0.4-15	[85,88,91,92]	1.68-980	[80,88]
Candida parapsilosis	1.69	[87]	13-27	[87,88]
Candida tropicalis	0.25-20	[81,82,87,88,92]	3.4-30	[80,87,88]
Candida krusei	0.125-0.84	[81,82,88]	13-30	[80,88]
Cryptococcus gattii	0.84	[88]	0.84	[88]
Cryptococcus neoformans	0.25-8	[81,83,84,88]	0.42	[88]
Fusarium moniliforme	4	[82]	/	/
Fusarium oxysporum	2-16	[82,84]	/	/
Fusarium solani	1-2	[81,82]	/	/
Microsporum canis	200	[94]	/	/
Microsporum gypseum	170	[94]	/	/
Penicillium notatum	31.2	[95]	/	/
Saccharomyces cerevisiae	12	[96]	/	/
Sporothrix schenckii	0.25	[81]	/	/
Trichophyton mentagrophytes	5-180	[79,94]	/	/
Trichosporon ashii	0.5	[97]	/	/

fungal species but cannot be used to predict their performance definitively.

Despite the documented antimycotic properties of Ag NPs, few overarching conclusions about how Ag NPs should be designed for maximum antimycotic activity can be drawn. This is because many physiochemical properties such as size, shape, and surface chemistry influence the antifungal properties of the particles, but these parameters have not been rigorously and systematically explored to elucidate their structure-function relationship in the antimycotic space. However, one consistent trend is that smaller Ag NPs generally have greater antifungal efficacy [98]. This is consistent with observations of the activity of Ag NPs against bacteria which also tends to increase as their size decreases [99]. Ag NPs are commonly thought to exert their antimicrobial effect through the release of soluble ions. As such, the superior antimicrobial properties of the smaller Ag NPs is often attributed, at least in part, to their higher specific surface area that leads to faster soluble ion release [99,100].

In addition to particle size, researchers have reported that the choice of particle stabilizer influences the antifungal activity of these NPs [87,101]. For instance, the antifungal activities of different surfactant- or polymer-stabilized Ag NPs were tested, with non-stabilized Ag NPs and ionic silver as controls [87]. In this work, all the Ag NPs were spherical with a mean size of 25 nm. The MIC values of the non-stabilized Ag NPs were 0.21-0.42, 1.68 and 0.84 μg/mL against *Candida albicans, Candida parapsilosis* and *Candida tropicalis*, respectively. By contrast, surfactant- or polymer-stabilized Ag NPs showed higher antifungal activity against the same fungal strains, with lower MIC values of 0.052-0.21, 0.84 and 0.42 μg/mL, respectively. The authors ascribed the better antifungal activity of stabilized Ag NPs to the improved colloidal stability of the particles and the antimicrobial activity of the stabilizing surfactants themselves.

While some research has shown significant differences in antifungal properties among Ag NPs of different sizes and surface chemistries, there is debate in the literature. For instance, some researchers found that particle size and stabilization method had no significant effects on the antifungal activity of Ag NPs [91]. Monteiro et al. synthesized Ag NPs of different sizes (5, 10 and 60 nm) and used two different stabilizers, ammonia and polyvinylpyrrolidone (PVP) [91]. The researchers found relatively consistent MIC values against *Candida albicans* (0.4-0.8μg/mL) and *Candida glabrata* (0.8-3.3 μg/mL). These results were rationalized by an aggregation argument. It was postulated that the particles aggregated on the surface of the microorganism before exerting their antimicrobial properties. As such, it would be the size of the aggregate, not the individual particles, that dictates the antimicrobial properties [102]. However, experimental evidence was not provided to support this claim.

Most of the data on the antifungal properties of Ag NPs is on fungal dispersions. However, fungi often exist in biofilms and in complex biological environments. While little work has focused on the impact of Ag NPs in these complex environments, the existing data is promising. For instance, in one study Ag NPs inhibited biofilm formation and destroyed pre-existing biofilms [85]. Additionally, Ag NPs coated onto contact lenses were shown to exhibit antifungal properties in an eye infection model. Briefly, Ag NPs (25-50 nm) were coated on the contact lens surfaces using dopamine as both a reducing agent and an adhesive (AG@PDA-2.5) (Fig. 3(a) and (b)) [103]. The Ag NP coatings were stable, exhibiting no significant changes after 20 min of ultrasonic cleaning (Fig. 3(c)). Additionally, the Ag NP-coated contact lenses exhibited good therapeutic effects in rabbits with fungal keratitis induced by *Aspergillus fumigatus*. After 3 days post-infection, the rabbits' eyes in the control group became cloudy, while those with the Ag NP coated-contact lens remained clear. After 16 days, the rabbits' eyes in the control group were uniformly opaque and showed heavy hyphemia, while that in the Ag NP-coated group still had a discernible pupil (Fig. 3(d)). Hematoxylin and eosin staining of the eyes indicated that the cornea pathology was significantly ameliorated in the Ag NP-coated lens group compared to the control group (Fig. 3(e)). These data illustrate the potential of Ag NPs to combat fungal infections, specifically as coatings on medical devices, and support the case for further research.

Ag NPs were reported to be more effective on a mass basis than many antifungal drugs, such as amphotericin B, fluconazole, ketoconazole, natamycin, griseofulvin, itraconazole, among others [79,81,82,97]; for instance, Ag NPs showed higher antibacterial efficacy than amphotericin B against *Candida albicans* [92,104,105], *Candida tropicalis* [104], and *Saccharomyces cerevisiae* [92,105].

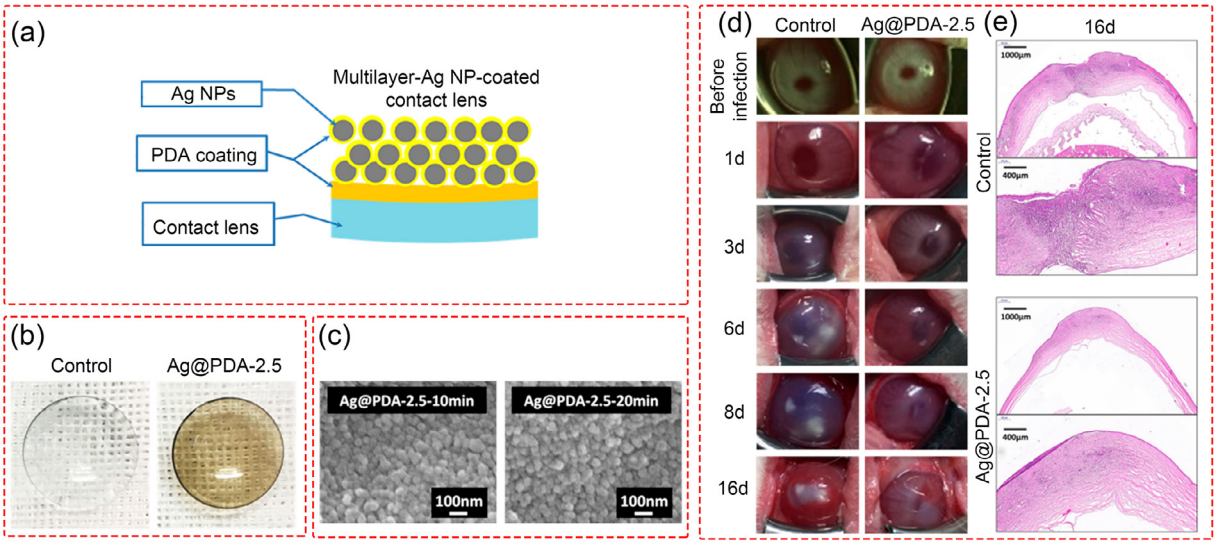

Fig. 3. Multilayer-Ag NPs-coated contact lenses for early treatment of bacterial and fungal keratitis: (a) schematic of multilayer Ag NPs coating; (b) photographs of contact lenses with and without Ag NP coating; (c) SEM images of Ag NP coated contact lenses after 10 and 20 min ultrasonic cleaning; (d) photographs of rabbit eyes infected with *A. fumigatus*; (e) hematoxylin and eosin staining of rabbit eyes following 16 days of infection with *A. fumigatus* with and without Ag NP coated contact lens treatment [103]. (Adapted with permission from A mussel-inspired facile method to prepare multilayer-AgNP-loaded contact lens for early treatment of bacterial and fungal keratitis. X. Liu; J. Chen; C. Qu; G. Bo; L. Jiang; H. Zhao; J. Zhang; Y. Lin; Y. Hua; P. Yang. *ACS Biomaterials Science & Engineering* 2018, *4* (5), 1568-1579. Copyright 2018, American Chemical Society.)

Wang et al. found that 16 nm Ag NPs had a significantly lower MIC than itraconazole against *Fusarium spp.* and lower MIC than fluconazole against eight fungal strains [82]. Atef et al. reported that Ag NPs had lower MIC values than antifungal drugs griseofulvin and Itraconazole against *Candida albicans* and *Trichophyton mentagrophytes* [79]. Xia et al. found that the MIC value of Ag NPs against *Trichosporon ashii* was 0.5-1 μg/mL, which is lower than some antifungal drugs including amphotericin B, 5-flucytosine, caspofungin, terbinafine, fluconazole, and itraconazole, but higher than voriconazole [97].

Although the antifungal properties of Ag NPs are impressive, most of above-mentioned studies have only tested the antifungal efficacy of Ag NPs, and few have also assessed their toxicity to mammalian cells. When this has been investigated, many studies have shown the significant cytotoxicity of Ag NPs relative to the doses required to prevent fungal growth. For example, 20-25 nm Ag NPs exhibited MICs of 25 μg/mL, 6 μg/mL and 3 μg/mL against *Aspergillus niger, Candida albicans*, and *Cryptococcus neoformans*, respectively. However, just 3 μg/mL of these Ag NPs caused approximately 60% death of human cells (THP-1), leaving no therapeutic window [83]. In another report, 35-55 nm Ag NPs showed a MIC of 31.2 μg/mL against *Penicillium notatum*, but the IC50 (the dose at which cell viability falls to 50%) were only 2.5 μg/mL and 5.3 μg/mL to human breast epithelial cell line MCF7 and monkey kidney epithelial VERO cells, respectively [95]. It has also been reported that 30 μg/mL Ag NPs with mean size of 25 nm can cause 100% death of human fibroblasts [87]. Nonetheless, there are a handful of studies that reported more promising results. Ag NPs with mean size 9.8 nm exhibited MIC of 0.4-0.5 μg/mL against *Candida* species, and human lung cell line MRC5, human vascular endothelial cells (HUVECs) and Chinese hamster ovary cells (CHO) retained viability higher than 80% after treatment with 2 μg/mL of these NPs. However, the viabilities of these cells decreased sharply to lower than 60% when treated with 3 μg/mL Ag NPs [106]. Silva et al. found that the concentrations of Ag NPs with a mean size of 16 nm required to inhibit 90% of growth (MIC_{90}) were 2.7 μg/mL and 0.54 μg/mL against *Trichophyton rubrum* and *Trichophyton mentagrophytes*, respectively [107]. The viability of keratinocyte epithelial cells at least 80% after 48 h with these Ag NPs at concentrations up to 2.7 μg/mL. Another study reported the MFC of Ag NPs with mean size of 19 nm as 0.25-0.5 μg/mL against fluconazole-resistant *Candida* species, and 1.1 μg/mL of these Ag NPs only induced a 7% decrease in viability of NIH/3T3 fibroblasts [108]. Strangely, the report did not mention how long the cells were treated with the Ag NPs. Although these *in vitro* works reported the safe doses of Ag NPs for mammalian cells were higher than their MIC values, these studies are still too limited and variable to confidently identify a useful therapeutic window of Ag NPs for fungal infection treatments. Thus, the feasibility of clinical application of these Ag NPs for antifungal applications is still unclear, and more investigations are required to understand the mechanisms of toxicity following various modes and durations of exposure to Ag NPs.

4.2. Gold nanoparticles

Compared to Ag NPs, the potential use of gold nanoparticles (Au NPs) for antifungal applications has received much less experimental attention. Most of the Au NPs used in these antifungal studies were synthesized using so-called green methods with biological products as the reducing agents, such as plant extracts [62,109,110], bacterial filtrate [111] or fungal filtrate [112]. They are generally in the size range of 20-300 nm and have shown antifungal activity against a wide range of fungal species, including *Candida albicans* [62], *Puccinia graminis tritici* [62], *Aspergillus flavus* [62,112], *Aspergillus niger* [62,110], *Aspergillus terreus* [112], *Fusarium Oxysporum* [110], *Microphyton gypseum* [111], and *Trichophyton rubrum* [111]. An agar diffusion assay was adopted for antifungal tests in most of these studies, which is generally qualitative, making quantitative assessments and comparisons difficult.

A few studies have provided quantitative antifungal results. One study fabricated two different sized Au NPs using different reducing agents, and found that the MIC_{80} of 25 nm and 30 nm Au NPs against *Candida* species were 16-32 μg/mL and 32-128 μg/mL, respectively [113]. This study indicated that the smaller Au NPs may have greater antifungal efficacy, and a similar tendency was found in some other studies [114,115]. Dananjaya et al. synthesized Au NPs (16-23 nm) using a polysaccharide solution extracted from

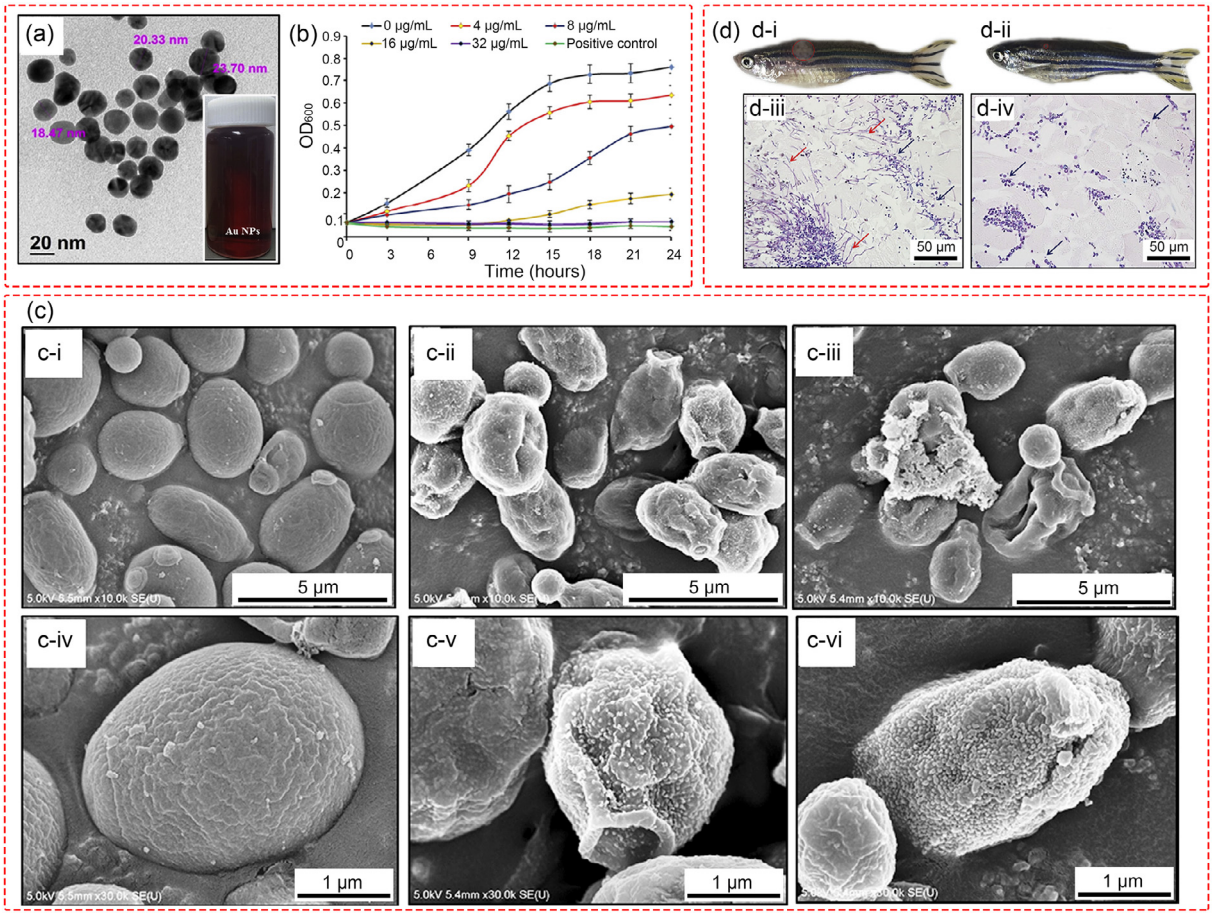

Fig. 4. (a) Transmission electron microscopy (TEM) image of Au NPs synthesized using a polysaccharide from *Spirulina maxima* alongside a photograph of the Au NP suspension; (b) growth curves of *C. albicans* after treatment with 0-32 µg/mL Au NPs at 30°C, shown as optical density at 600 nm; 10 µg/mL Nystatin (an antifungal drug) was used as the positive control; (c) low- and high-magnification FESEM images of *C. albicans*: (c-i, c-iv) untreated control, (c-ii, c-v) treated with 32 µg/mL Au NPs, and (c-iii, c-vi) treated with 64 µg/mL ; (d) Efficacy of Au NPs therapy on *C. albicans* infection in zebrafish dorsal muscle at 72 hpi h post-inoculation: photographs of control fish (d-i) and Au NP treated fish (32 µg per fish) (d-ii), with histopathological examination of *C. albicans* infection in control fish (d-iii) and Au NP treated fish (d-iv). The red and blue arrows point to the *C. albicans* hyphae and cells, respectively. Here, the infected site showed the invading yeast-hyphae and inflamed tissues with cell infiltration [116]. (Reprinted from *Process Biochemistry*, 92, S. Dananjaya; N. T. Thao; H. Wijerathna; J. Lee; M. Edussuriya; D. Choi; R. S. Kumar, *In vitro* and *in vivo* anticandidal efficacy of green synthesized gold nanoparticles using Spirulina maxima polysaccharide, 138-148, Copyright (2020), with permission from Elsevier.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cyanobacteria as the reducing agent (Fig. 4(a)), and these Au NPs exhibited a MIC value of 32 µg/mL (Fig. 4(b)) and a MFC value of 64 µg/mL against *Candida albicans*, which showed notable morphological changes after treatment with Au NPs (Fig. 4(c)) [116]. An *in vivo* test was performed to examine the effect of these Au NPs on *C. albicans* replication in zebrafish (Fig. 4(d)). The zebrafish were injected into the dorsal muscle with *C. albicans* cells; at 72 h post-inoculation (hpi), the control fish showed severe fungal growth (Fig. 4(d-i)), while fish treated with Au NPs showed less fungal growth at the injection site (Fig. 4(d-ii)). The fungal infection in the treated fish disappeared by 120 h post-inoculation. Histopathological analysis at 72 hpi showed that the control fish had an extensive growth of *C. albicans* hyphae (Fig. 4(d-iii)) compared to the treated fish (Fig. 4(d-iv)).

The antifungal mechanism of Au NPs is thought to operate via membrane damage and enzyme inactivation. For instance, damage of fungal cell membranes has been observed after treatment with Au NPs [116]. They may also interact with the transmembrane protein H^+-ATPase, an ATP-driven enzyme that transforms the energy from ATP hydrolysis to electrochemical potential differences across diverse biological membranes via the primary active transport of H^+. The proton gradients are used to drive secondary transport processes, essential for the growth of the fungal cell. Au NPs can interact with H^+-ATPase and disturb its activity, which in turn affects the metabolism of the fungus and leads to the death of fungi [113].

Assessment of cytotoxicity is once again very rare in these antifungal Au NPs research studies. In the paper described above, cytotoxicity analysis of Au NPs was done using human embryonic kidney cells HEK293T and human lung adenocarcinoma epithelial cells A549. After 24 h treatment these Au NPs showed no cytotoxic effects towards these two cell lines up to 64 ug/mL, which is the MFC value of these Au NPs against *Candida albicans* [116]. The result seems promising, but testing at higher doses would also be needed. Future studies should include both antifungal studies and toxicity studies towards relevant human cells. Therefore, it is unknown whether Au NPs can be safely used as antifungal agents in clinical therapies.

4.3. Copper nanoparticles

Copper nanoparticles (Cu NPs) were reported to have antifungal activities against many different types of fungi, including *Alternaria alternate, Aspergillus flavus, Aspergillus niger, Candida albicans, Candida tropicalis, Corticium salmonicolor, Curvularia lunata, Fusarium equiseti, Fusarium oxysporum, Fusarium culmorum, Phoma*

Table 3
MIC and MFC values of ZnO NPs against a variety of fungal strains.

Fungal strains	MIC (μg/mL)	Refs.	MFC (μg/mL)	Refs.
Alternaria alternata	64	[144,145]	/	/
Aspergillus flavus	156	[146]	312	[146]
Aspergillus niger	12.5-16	[141,144,145]	12.5	[141]
Botrytis cinerea	128	[144,145]	/	/
Candida albicans	6.25-200	[141,147–149]	6.25-2000	[141,142,148–150]
Fusarium oxysporum	64	[144,145]	/	/
Malassezia pachydermatis	200	[147]	/	/
Penicillium expansum	128	[144,145]	/	/

destructive and *Stachybotrys chartarum* [64,117–123]. Comparing to Ag NPs, Au NPs and ZnO NPs, antifungal studies on Cu NPs have been quite superficially reported. Most of the Cu NPs in these reports were fabricated through chemical reduction methods with particle sizes in the range of 2-350 nm. As discussed above, the agar diffusion method adopted for antifungal tests in most of these studies which has inherent limitations. Nevertheless, Cu NPs were reported to have high antifungal efficacy with relatively low MIC against different fungal species. For example, Cu NPs (9-34 nm) synthesized by thermal decomposition showed MIC of approximately 2.5 μg/mL against *Stachybotrys chartarum* [64]; ultrafine Cu NPs (2-4 nm) obtained by chemical reduction exhibited MIC of 7 μg/mL against *Corticium salmonicolor* [123]; and carboxymethylated chitosan-stabilized Cu NPs (4-15 nm) fabricated by chemical reduction exhibited MIC of 3.9 μg/mL against *Candida tropicalis* [122]. Additionally, Cu NPs have been coated on a variety of polymer surfaces including PVDF, PVC, and PVMK, with promising antifungal results [124,125]. However, data on the cytotoxicity of Cu NPs is once again scarce in antifungal studies. Tantubay et al. reported that L929 fibroblasts only experienced a relatively slight decrease of 5% in cell viability after 24 h treatment with Cu NPs at their MIC (3.9 μg/mL) against *Candida tropicalis* [122]. Although these results indicated the promising potential of using Cu NPs for antifungal applications, more thorough testing with different species of fungi and *in vivo* tests should be conducted to better assess the potential and biosafety of Cu NPs for antifungal use.

4.4. Zinc oxide nanoparticles

Zinc oxide nanoparticles (ZnO NPs) are the most widely researched metal oxide NPs for antifungal applications. Part of the reason for their prominence in the literature is the fact that fungicides commonly used in agriculture are mainly made of zinc compounds [63]. Zinc is an essential element to human beings, and ZnO is even provided directly to consumers as daily zinc supplements. ZnO NPs have been shown to have good biocompatibility towards human cells, and the 50% lethal dose (LD_{50}) of oral toxicity for ZnO is relatively high (240 mg/kg in rats) [56,126].

ZnO NPs have been found to have antifungal activity against a broad range of fungal species, including *Alternaria alternata* [127], *Alternaria solani* [128], *Aspergillus aculeatus, Aspergillus brasiliensis* [129], *Aspergillus flavus* [130], *Aspergillus fumigatus* [131], *Aspergillus niger* [131], *Aspergillus nidulans* [130], *Botrytis cinereal* [132], *Candida albicans* [133], *Erythricium salmonicolor* [134], *Fusarium oxysporum* [127], *Fusarium graminearum* [135], *Microsporum canis* [136,137], *Mucor plumbeus* [127], *Fusarium sp.* [138], *Penicillium expansum* [132], *Pythium debaryanum* [139], *Rhizopus stolonifer* [127], *Sclerotium rolfsii* [128,139], *Trichoderma harzianum* [130], and *Trichophyton mentagrophytes* [136,137]. The MIC and MFC values of ZnO NPs against different types of fungi are summarized in Table 3. The sizes of the ZnO NPs used in studies cited in this table were 12-65 nm. The antifungal activity of ZnO NPs has been investigated in a concentration-dependent manner [140], in addition to studies which varied the sizes and shapes of the nanoparticles [134,135,139]. The relationship between the nanoparticle size and its antifungal activity is not clear; some research showed smaller ZnO NPs had higher antifungal activity [135]. while others found the opposite was true. For example, ZnO NPs with a mean size of 65 nm exhibited a MFC value of 6.25 μg/mL against *C. albicans*, much lower than the 100 μg/mL of 11.6 nm ZnO NPs [141,142]. Some studies have also claimed that particle size has no significant effect on the antifungal activity of ZnO NPs [139,143]. The antifungal activities against *Alternaria alternata, Aspergillus niger, Botrytis cinerea, Fusarium oxysporum* and *Penicillium expansum* of green synthesized ZnO NPs (12-32 nm) and chemically synthesized ZnO NPs (12-63 nm) were also compared, and no significant difference was found, indicating that any differences due to size in these ranges did not have a large impact on the results [144,145].

ZnO NPs were reported to have better antifungal activities than silica and other metal oxide NPs. Karimiyan et al. compared the antifungal activity of several metal oxide NPs against *C. albicans*, including ZnO NPs (20 nm), MgO NPs (40 nm), SiO_2 NPs (10 nm) and CuO NPs (60 nm), and found that the ZnO NPs were most effective. The MIC and MFC values for ZnO NPs against *C. albicans* were only 200 μg/mL and 400 μg/mL, respectively. By contrast, both the MIC and MFC values were 400 μg/mL for CuO NPs, and were each higher than 3200 μg/mL for both MgO NPs and SiO_2 NPs [148]. All of the metal oxide NPs studied were far less effective on a mass basis than the antifungal drug amphotericin B, which showed MIC and MFC values of only 0.5 μg/mL and 2 μg/mL, respectively [148]. Deforming fungal hyphae, distorting and damaging conidia, and promoting ROS production were all reported as antifungal mechanisms of ZnO NPs [132,134,143,146]. More detailed mechanisms are described below in Section 5.

The cytotoxicity of ZnO NPs was rarely reported in the papers mentioned above. Miri et al. reported that the IC_{50} of 40-50 nm hexagonal ZnO NPs to breast cancer cells (MCF7) was 500 μg/mL, and the cell viability decreased to lower than 70% at only 31 μg/mL, which is lower than their MIC (32-64 μg/mL) and MFC (128-512 μg/mL) against *C. albicans* [149]. From these results, the clinical application of these ZnO NPs as antifungal agents could be limited.

4.5. Titanium dioxide nanoparticles

Titanium dioxide nanoparticles (TiO_2 NPs) have shown relatively low toxicity against mammalian cells and have a record of use in consumer products such as sunscreens [65,151]. They also exhibit antifungal properties against various fungal species such as *Candida albicans* [152] and *Fusarium oxysporum* [65]. TiO_2 NPs with sizes of 70-100 nm, synthesized through the hydrolysis of titanium tetrachloride ($TiCl_4$), showed significant inhibition of biofilm formation on both fluconazole-sensitive and -resistant *C. albicans* at 5 μg/mL [152]. It is hypothesized that the antimicrobial activity of TiO_2 NPs is derived through their photocatalytic activity. Darbari et al. tested this theory by coating TiO_2 NPs on branched car-

bon nanotubes (CNTs), finding that, in the presence of visible light, there was clear evidence of photocatalytic antifungal effects leading to the photodegradation of *C. albicans* biofilms. The authors considered that the CNTs doped with TiO_2 NPs had a band gap smaller than that of pure TiO_2, which caused the CNT/TiO_2 interface to lead to excitation enhancement under visible light, and subsequently the generation of an electron hole in TiO_2. The photogenerated holes could result in the generation of OH radicals on the surface of the microorganism, which could damage the cells [153]. However, in most cases TiO_2 NPs use ultraviolet light (2-3% of sunlight) as an irradiation source, which limits the antimicrobial effects of TiO_2 NPs [154]. Nitrogen and fluorine co-doped TiO_2 NPs can take advantage of the whole spectrum of visible-light irradiation to produce ROS, which in turn gives them relatively effective antifungal activity in the presence of visible light [65]. Further investigation is necessary to evaluate the toxicity of these doped antifungal TiO_2 NPs towards mammalian cells.

4.6. Iron oxide nanoparticles

Iron oxide NPs, including maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4) NPs have grown in popularity in recent years, as they have proved their worth as a versatile and safe nanomaterial for biomedical applications. They are widely favoured due to their biodegradability, low cytotoxicity, and their active surfaces that can be altered with biocompatible coatings [155]. Research on iron oxide NPs has mostly been focused on their magnetic capabilities, which have been utilized for medical diagnostic imaging [156], targeted drug delivery [157], and various other biofabrication and therapeutic applications [158,159]. However, recent studies have also investigated the potential antifungal and antibacterial applications of these nanoparticles [66]. Fe_2O_3 NPs with sizes of 10-30 nm, synthesized using tannic acid as both a reducing agent and stabilizer, showed MIC of 16-63 ug/mL against *Alternaria alternata, Aspergillus niger, Cladosporium herbarum, Penicillium chrysogenum* and *Trichothecium roseum* [160]. Fe_3O_4 NPs were found to have some relevant antifungal activity against *Candida species*, with MIC and MFC values of 62.5-500 μg/mL and 500-1000 μg/mL, respectively [161]. Fe_3O_4 NPs also showed inhibitive effects on fungal biofilm formation; specifically, Fe_3O_4 NPs at 50 μg/mL caused around 70% inhibition of biofilm produced by *Candida albicans*, and it reached 100% inhibition of biofilm formation at 200 μg/mL [162]. Metallocarbonyl-functionalized Fe_3O_4 NPs at 50 μg/mL were also reported to reduce approximately 70% of the biofilm mass formed by flucytosine-resistant *Candida albicans*; the authors hypothesized that this change was due to the presence of Fe_3O_4 NPs improving the sensitivity of cells in the biofilm matrix to the metallocarbonyl complexes, by affecting the cell viability and reducing the biofilm mass [163]. The antifungal mechanisms of iron oxide NPs are still far from being fully understood and more research is required. The toxicity towards mammalian cells of the specific iron oxide NPs being considered for antifungal applications also needs to be determined, as important properties, such as their size, shape, and surface chemistry, may differ from the NPs used in other biomedical applications.

4.7. Transition-metal dichalcogenide nanoparticles

Recently, transition-metal dichalcogenide nanoparticles (TMDC NPs) were found having great promise in antimicrobial activity. It is reported that molybdenum disulfide (MoS_2) nanosheets showed certain antifungal activity against *Alternaria alternata* by ROS generation under ambient light. Unfortunately, the study did not specify the amount of MoS_2 used for antifungal tests [164]. Saha et al. prepared molybdenum diselenide ($MoSe_2$) nanosheets dispersed in the cationic polymer chitosan (CS) using a sonication method, as shown in Fig. 5(a) [165]. The $MoSe_2$/CS nanosheets had an average area and thickness of 2449 nm^2 and 8.7 nm, respectively. They exhibited MIC of 0.78-37.5 μg/mL and MFC of 6.25-75 μg/mL for diverse filamentous and yeast strains, including *Aspergillus fumigatus, Candida parapsilosis, Candida albicans, Cryptococcus gattii, Cryptococcus neoformans, Issatchenkia orientalis*, and *Saccharomyces cerevisiae*, while the safe concentration of the $MoSe_2$/CS nanosheets was considered to be 150 μg/mL based on an *in vitro* hemolysis assay and a cytotoxicity assay towards human embryonic kidney (HEK 293) cells. The $MoSe_2$/CS nanosheets were considered to induce fungal cell death by causing membrane damage, membrane depolarization, metabolic inactivation and cytoplasmic leakage. As Fig. 5(b) shows, the bright red fluorescence arises from the FUN 1 cell stain coming from the cytoplasm of metabolically active cells, where they form dense aggregates, whereas metabolically inactive fungal cells were indicated by the absence of bright red aggregates. The SEM images showed that fungal cells treated with $MoSe_2$/CS nanosheets exhibited distinct membrane damage, breaking of filaments and deformed cells (Fig. 5(c-i, c-ii, d-i and d-ii)), while TEM images further confirmed membrane damage and cytoplasm leakage (Fig. 5(c-iii, c-iv, d-iii and d-iv)).

Although the research on antifungal $MoSe_2$/CS nanosheets seems promising, the research on antifungal TMDC NPs has only begun in the last few years, and the antifungal efficacy and biosafety of such NPs need to be explored further.

4.8. Selenium nanoparticles

Similar to zinc, selenium is a nutritional element for humans, making it an attractive material to investigate for antimicrobial applications [166]. In this vein, the antimicrobial activity of selenium nanoparticles (Se NPs) has been increasingly researched in the past decade, with promising results demonstrated, particularly for antibacterial applications [58,166–169]. Se NPs have been reported to have antifungal activities against *Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Candida albicans, Candida glabrata, Candida krusei, Candida tropicalis*, and *Trichophyton rubrum* [67,170–173]. Interestingly, Se NPs used in some of these reports were biosynthesized intracellularly in bacteria. For example, Se NPs with sizes of 90-320 nm, biosynthesized by the Gram-negative bacteria *Klebsiella pneumoniae,* exhibited MICs of 250 μg/mL and 2000 μg/mL against *Aspergillus niger* and *Candida albicans*, respectively [67]. Se NPs with sizes of 120-140 nm, biosynthesized by the Gram-positive bacteria *Bacillus* species Msh-1, showed MICs of 100 μg/mL and 70 μg/mL against *Aspergillus fumigatus* and *Candida albicans*, respectively [172]. Cremonini et al. biosynthesized Se NPs using both the Gram-positive bacteria *Bacillus mycoides* and the Gram-negative bacteria *Stenotrophomonas maltophilia*, and obtained particle mean sizes of 161 ± 52 nm and 171 ± 35 nm, respectively. These Se NPs showed MIC of 512 μg/mL and 256 μg/mL against *Candida albicans*, respectively [173]. On the other hand, up to 500 μg/mL of these particles did not show any toxicity to human dendritic cells and human primary fibroblasts, and at concentrations below 250 μg/mL they did not induce a significant increase in the release of pro-inflammatory and immunostimulatory cytokines. These results indicated promise for the use of Se NPs at safe doses for antifungal applications. The antibiofilm activity of Se NPs was also reported. The above-mentioned biosynthesized Se NPs displayed approximately 60% and 80% inhibition of *Candida albicans* biofilm formation at 50 μg/mL and 400 μg/mL, respectively [173]. Chitosan-capped Se NPs with a mean size of 96 nm showed a potent inhibitory effect against a pre-formed *C. albicans* biofilm in a dose-dependent manner, with 50% inhibition occurring at 3.5 μg/mL and approximately 80% inhibition occurring at 10 μg/mL. The IC50 of these chitosan-capped Se NPs was found to be 26.3 μg/mL towards retinal pigment epithelial cells (derived from the cell line ARPE-

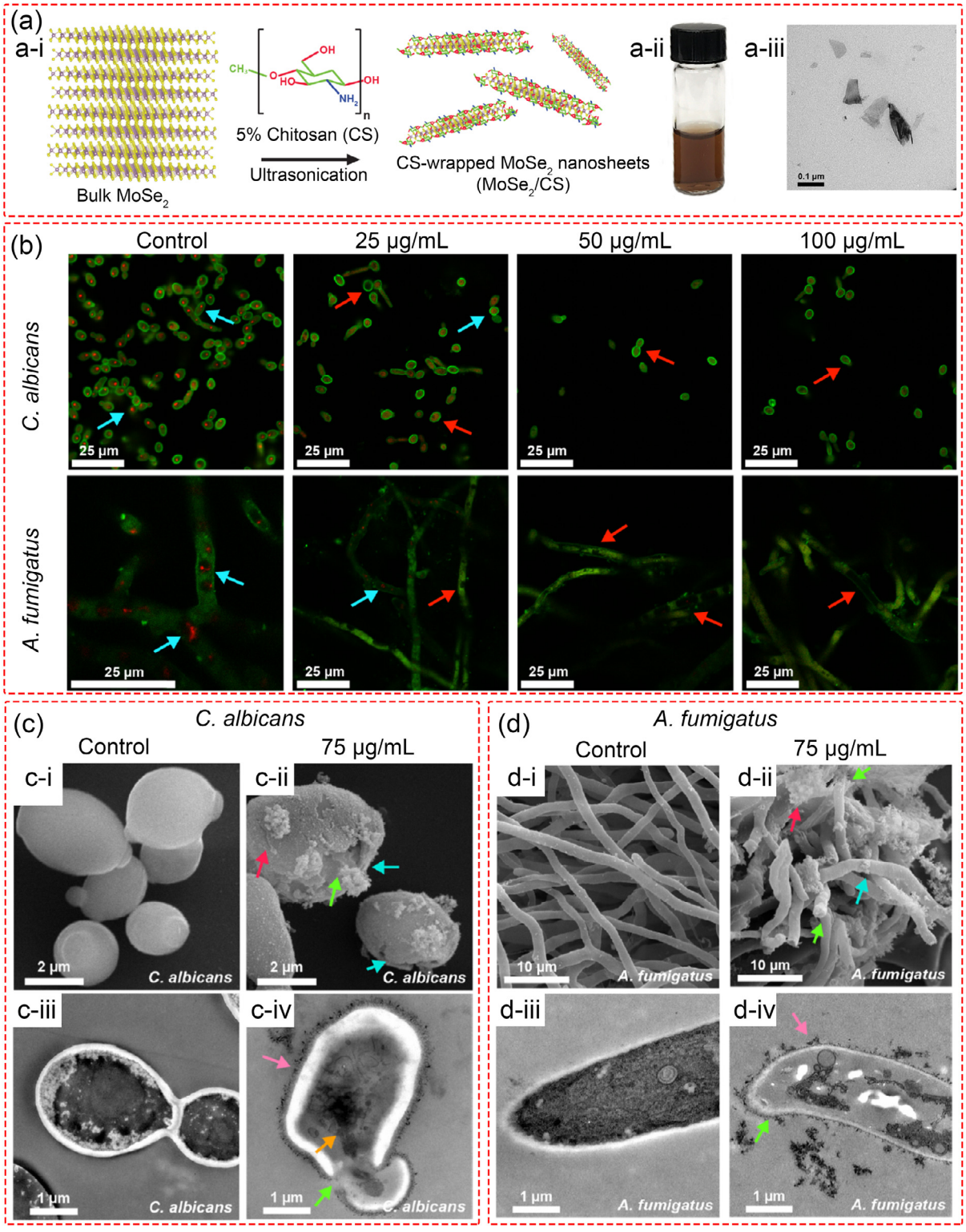

Fig. 5. (a) Schematic illustration of fabrication process of $MoSe_2$/CS nanosheets (a-i) and the photograph of the obtained $MoSe_2$/CS nanosheets dispersion (a-ii) as well as the TEM image of $MoSe_2$/CS nanosheets (a-iii). (b) Fluorescence images of fungal cells by confocal scanning laser microscopy, the green colour shows the fungal cell walls and red colour shows the metabolically active cytoplasm. The viable cells are pointed with cyan arrows. The absence of red aggregates in the cells signifies loss of viability or dead cells (red arrows pointed). (c) are SEM (c-i and c-ii) and TEM (c-iii and c-iv) images of *C. albicans* after treatment with $MoSe_2$/CS nanosheets. (d) are SEM (d-i and d-ii) and TEM (d-iii and d-iv) images of *A. fumigatus* after treatment with $MoSe_2$/CS nanosheets [165]. (Adapted with permission from S. Saha; M. S. Gilliam; Q. H. Wang; A. A. Green, Eradication of Fungi Using $MoSe_2$/Chitosan Nanosheets, *ACS Applied Nano Materials* 2022, 5 (1), 133-148. Copyright 2022 American Chemical Society.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

19) and the cells' viability was higher than 80% at concentration of 10 μg/mL [168]. This result further supported the promising therapeutic window of Se NPs for antifungal applications. The antifungal mechanisms of Se NPs that have been reported so far include membrane destruction and influence on the expression of proteins [168,174].

4.9. Carbon-based nanomaterials

Carbon nanomaterials are widely researched in biomedicine, energy, and sensing fields [175], but the number of reported antifungal studies is very limited. Graphene oxide (GO), fullerenes (C_{60}), and carbon nanotubes (CNTs) were the most researched carbon-based antifungal nanomaterials. These carbon-based nanomaterials were found to have significant antifungal activities against *Fusarium graminearum, Fusarium poae* and *Botrytis cinerea* [176–178]. It is reported that the carbon atom content enables the destruction of pathogen cell walls [179], and these carbon nanomaterials can pass through the cell membranes to reach to the cytoplasm of the pathogens. CNTs were reported to be able to alter oxidative enzyme activities [180], and GO is able to reduce mycelial biomass and branching, and alter proteins, lipids and other metabolites in fungal cells [176].

Although the antifungal properties of carbon nanomaterials have been reported in some literature, to the best of authors' knowledge, no quantitative antifungal studies of plain carbon nanomaterials (without combining with other antifungal agents) were reported so far, and the quantitative antifungal efficiency (MIC and MFC values) of carbon nanomaterials based on standard test methods needs to be assessed [181]. Also, these carbon nanomaterials often induce distinct toxicity towards mammalian cells and activate different immune cells. Therefore, the application of these carbon nanomaterials in human and animal health care may be challenging [182]. Most of the reported studies to date were focusing on applying these antifungal carbon-based nanomaterials in plants. Using carbon nanomaterials for the treatment of fungal infections in humans and animals should be further studied to explore their application prospects in this field.

4.10. Other nanoparticles

Apart from the NPs already discussed in this review, a variety of other types of NPs of interest have been explored as potential antifungal agents. Nanoparticles made from platinum and palladium, which are noble metals like gold and silver, also showed antifungal activity. Velmurugan et al. fabricated platinum (Pt) NPs with sizes of 10-50 nm and found that they were efficient antifungal agents against *Colletotrichum acutatum* and *Cladosporium fulvum* [183]. Palladium (Pd) NPs with different mean sizes from 200 nm to 550 nm were fabricated and their antifungal properties against *Colletotrichum gloeosporioides* and *Fusarium oxysporum* were investigated [184]. It was found that the size of Pd NPs played a critical role in their antifungal activity, with the smallest of these particles showing the highest antifungal efficacy. Pd NPs larger than 350 nm did not show antifungal effect against *Colletotrichum gloeosporioides*. Unfortunately, these works did not quantify the antifungal activity of these nanoparticles or explore their antifungal mechanisms. The cytotoxicity of these Pd NPs towards mammalian cells has not been evaluated, to the author's knowledge.

Some antifungal bimetallic and trimetallic NPs have been reported in recent years [185–188]. They were synthesized by mixing metal salts as precursors with plant extracts, which acted as both reducing agents and particle stabilizers. The results showed that the multimetallic NPs had relatively low MIC and MFC against non-drug resistant *Candida albicans* and *Candida auris*, with MIC lower than 5 μg/mL and MFC lower than 10 μg/mL. Ag-Ni and Ag-Cu NPs also exhibited antifungal activity against fluconazole-resistant *Candida albicans*. These multimetallic NPs can induce cell apoptosis, cell cycle arrest in G2/M phase and disturbances in primary and secondary antioxidant enzymes [185,188]. However, these NPs at their MIC or MFC induced haemolysis at much higher rates than the acceptable criterion of 5%, according to ASTM standard F7560-08 [189], leaving no therapeutic window. The cytotoxicity of these multimetallic NPs towards mammalian cells other than blood cells has not been reported to the author's knowledge. Thus, the value of developing antifungal multimetallic nanoparticles is not clear at present.

Some other metal oxide NPs have been researched for antifungal applications. CuO NPs were also reported to have antifungal activity against *Candida albicans* [190], *Candida glabrata* [191], *Candida tropicalis* [191], *Fusarium culmorum* [192], *Aspergillus niger* [193], and *Aspergillus flavus* [193]. However, their antifungal activity is relatively low, requiring a very high concentration (1000 μg/mL) to cause around 85% growth inhibition of *Aspergillus niger and Aspergillus flavus* [193]. The antifungal efficacy of CuO NPs has been even poorer when used as coatings; for example, with CuO NP-coated polycaprolactone (PCL) fibres, very high concentrations (~8000-16000 μg/mL) of the CuO NPs only resulted in around 50% growth inhibition of *Candida* species [191]. Aluminium oxide (Al_2O_3) NPs and magnesium oxide (MgO) NPs were reported to have potential antifungal activity against *Fusarium oxysporum* [194,195]. Zirconia (ZrO_2) NPs exhibited growth inhibition effects against *Candida albicans* and *Aspergillus niger* [196]. Unfortunately, there are only qualitative studies on the antifungal properties of these particles, without quantitative results. The antibacterial effectiveness of these particles is unknown, and their antifungal mechanism remains to be investigated. Bismuth trioxide (Bi_2O_3) NPs at 311 μg/mL displayed antifungal activity against *Candida albicans* with 85% inhibition of growth and a complete inhibition of biofilm formation. The MIC value of Bi_2O_3 NPs against *Candida albicans* was 699 μg/mL [197]. Although the authors described that monkey kidney (Vero) cells with and without treatment of Bi_2O_3 NPs at 932 μg/mL showed no difference in DAPI stained images, additional work is required to confirm that the Bi_2O_3 NPs are not toxic to mammalian cells.

Among the inorganic and non-metallic elements, many of the chalcogens have been explored to make antifungal NPs. In addition to the Se NPs discussed above, sulfur (S) NPs and tellurium (Te) NPs were also researched for antifungal applications. S NPs were reported to have promising inhibitory effects on the fungal growth and sporulation of *Aspergillus niger* and *Fusarium oxysporum*, significantly reducing their phospholipid content; however, more than 1000 μg/mL was required to completely prevent spore germination [198]. This same study also indicated that smaller S NPs showed relatively higher levels of antifungal activity than larger ones. Rod-shaped Te NPs exhibited antifungal properties against *Candida albicans*, albeit with relatively high MIC and MFC values of 1000 μg/mL and 2000 μg/mL, respectively. It was suggested that Te NPs imparted their antifungal properties through inhibition of squalene monooxygenase [68]. None of the research in this section reported the toxicity of these NPs towards mammalian cells, so questions remain about their potential utility.

5. Nanoparticles as antifungal drug delivery vehicles

In addition to nanoparticles themselves being used as antifungal agents, they have potential to be used as vehicles for antifungal drug delivery. Organic nanoparticles have also been extensively explored for this purpose, as reviewed previously [199]. Herein, we focus on inorganic nanoparticles and their development as antifungal drug delivery vehicles.

5.1. Antifungal drug conjugated nanoparticles

5.1.1. Silica nanoparticles (SiO_2 NPs)

SiO_2 NPs have been widely researched for potential drug delivery applications, due in large part to the facile synthesis routes available to create SiO_2 NPs with high porosity, tuneable pore sizes in the micro- to mesopore range, and large specific surface areas. Although the antifungal efficacy of SiO_2 NPs themselves is low, using them as carriers of antifungal drugs has achieved very good results [148,200]. One study found that amphotericin B-functionalized SiO_2 NPs (with sizes of 5 and 80 nm) could kill several strains of *Candida* species, and their efficacy was higher than that of 10 nm Ag NPs [200]. Additionally, these particles could be reused for up to 5 cycles without losing their efficacy. Another study incorporated amphotericin B-immobilized SiO_2 NPs into dental resins, which showed long term antifungal activity and exhibited no toxicity to human skin fibroblasts and human umbilical vein endothelial cells [201]. Didodecyldimethylammonium bromide (DDAB), a quaternary ammonium cationic surfactant, was likewise coated onto SiO_2 NPs and showed higher antifungal activity than soluble DDAB against *Candida albicans*, with MIC values of 25 ± 4.5 μg/mL and 125 μg/mL, respectively. These particles were relatively stable as no measurable loss of antifungal activity was observed after 60 days of storage in suspension [202].

5.1.2. Silver nanoparticles

Although silver nanoparticles are already good anti-fungal agents on their own, their antifungal activity can be further improved by conjugating with antifungal drugs. For instance, Ag NPs conjugated with Miconazole exhibited higher antifungal efficacy against *Candida* species than either Ag NPs or Miconazole alone [106]. Meanwhile, Tutaj et al. directly used antifungal macrocyclic polyene amphotericin B (Am B) as both the reducing agent and the stabilizing agent to fabricate Ag NPs, finding that these Am B-Ag NPs exhibited much more effective growth inhibition of *Aspergillus niger, Candida albicans* and *Fusarium culmorum* than dodecanethiol-capped Ag NPs (with a mean size of 4 nm). The authors ascribed the high antifungal efficacy of Am B-Ag NPs to the synergistic effect between Am B and Ag^+ ions [203]. Shi et al. used iturin as both the reducing agent and the stabilizer to synthesize Ag NPs [73]. Iturin is a lipopeptide with antifungal activity produced by *Bacillus subtilis*. The iturin-Ag NPs showed better antifungal activity than iturin and poly-N-vinylpyrrolidone (PVP) stabilized Ag NPs, showing synergistic activity between iturin and Ag NPs. The MIC values of iturin-Ag NPs against *Candida albicans* were 1.25, 2.5 and 5 μg/mL at the fungal concentrations of 10^5, 10^6 and 10^7 CFU/mL, respectively. It was suggested that these iturin-Ag NPs could damage the fungal cell membrane and promote ROS production. The viability of human HaCaT cells remained higher than 80% after 24 h of treatment with these NPs at up to 10 μg/mL, which is higher than their MIC values against *Candida albicans*.

5.2. Silver NP coated particles

Because of the high antimicrobial activity of Ag NPs, they have also been used as coatings for other, larger particles to optimize them for potential antifungal applications. One study reported that 7 nm Ag NPs coated on 350 nm SiO_2 NPs (Ag@SiO_2 NPs, as shown in Fig. 6) showed 99.9% growth inhibition against *Botrytis cinereal* at 50 μg/mL [204]. Another study coated 5 nm Ag NPs on 70 nm Fe_3O_4 NPs (Ag@Fe_3O_4 NPs), which also showed significant antifungal activity against four *Candida* species [155]. This combination with magnetic nanoparticles may also provide benefits for targeted application and subsequent removal of these nanocomposites via an external magnetic field.

6. Synergistic effects of drugs and bioactive molecules and NPs

Besides conjugating antifungal drugs on nanomaterials, simply mixing antifungal drugs with nanomaterials or mixing two different nanomaterials has also been investigated as an effective approach to achieve synergistic antifungal effects, which are defined as the combined antifungal effects of at least two antifungal agents making an impact that is more significant than both of them could have shown individually [205]. For instance, many antifungal drugs were found to have synergistic effects with Ag NPs [206–208]. The combination of Ag NPs and fluconazole has thus far been the most researched of these pairings, and showed synergistic antifungal activity against a broad spectrum of fungi species, including *Aspergillus fumigatus, Aspergillus flavus, Candida albicans, Cryptococcus neoformans, Fusarium semitectum, Phoma glomerate, Phoma herbarum*, and *trichophyton rubrum* [206–208]. The MIC values of fluconazole, griseofulvin and biosynthesized Ag NPs individually against *Trichophyton rubrum* were 40, 0.8 and 10 μg/mL, respectively [208]. The antifungal activities of fluconazole and griseofulvin were increased in combination with Ag NPs, with MIC values against *T. rubrum* of 2.5 μg/mL Ag NPs + 10 μg/mL fluconazole, and 2.5 μg/mL Ag NPs + 0.2 μg/mL griseofulvin, respectively. The combination of Ag NPs and fluconazole caused a significant dose-dependent decrease in the viability of both initial and mature biofilms of *C. albicans*, while the Ag NPs alone exhibited no significant inhibitory effect on these biofilms [209]. The combination of the drugs nystatin or chlorhexidine digluconate with 5 nm Ag NPs also exhibited potential ability for biofilm disruption [210]. Synergistic effects of Ag NPs with the antifungal drug ketoconazole against *Aspergillus niger, Aspergillus fumigates, Aspergillus flavus,* and *Fusarium* species have also been reported [211].

Synergistic effects of antifungal drugs used in tandem with metal oxide NPs have been reported as well. The combination of ZnO and three different fungicides, carbendazim, mancozeb and thiram, showed interesting synergistic antifungal effects against several different fungal species [212]. CuO NPs combined with fluconazole showed significant synergistic activity against *Candida albicans*, with a MIC of 200 μg/mL CuO NPs in combination with 300 μg/mL fluconazole against *Candida albicans*, while the MICs for individual CuO and fluconazole were 900 μg/mL and >400 μg/mL, respectively [213]. A synergistic fungicidal effect of ZnO NPs and CuO NPs was reported against *Alternaria citri* as well [214]. The mechanism behind this synergistic effect needs further study to be understood.

7. Antifungal mechanisms of inorganic nanoparticles

Published reports have demonstrated a variety of different mechanisms by which inorganic nanoparticles exert their antifungal effects, including release of mycotoxic ions [54], damage to the membrane [93], protein [215], DNA [132], and other critical cellular components, ROS overproduction [216], and ATP depletion [217] (Fig. 7). It is well established that the antimicrobial effects of Ag^+ ions and Ag NPs with positive surface charge can be attributed due to the electrostatic interactions between Ag^+ ions and/or Ag NPs with the negatively charged cell membrane. As a result, Ag NPs frequently attach to the cell membrane and/or penetrate inside the microorganism, causing changes in cellular structure, disrupting the cell wall and cytoplasmic membrane and inducing intracellular component leakage, damaging proteins, DNA and other cellular contents, and increasing the production of reactive oxygen species (ROS) which leads to mitochondrial dysfunctional apoptosis [79,88,93,216,218–224]. Apart from the antifungal activity of the Ag NPs themselves, Ag^+ ions released from the NPs could also exhibit antifungal effects [54,218,225]. Vazquez-Muñoz et al. evaluated the antifungal effects of Ag NPs (3-60 nm) against *Candida*

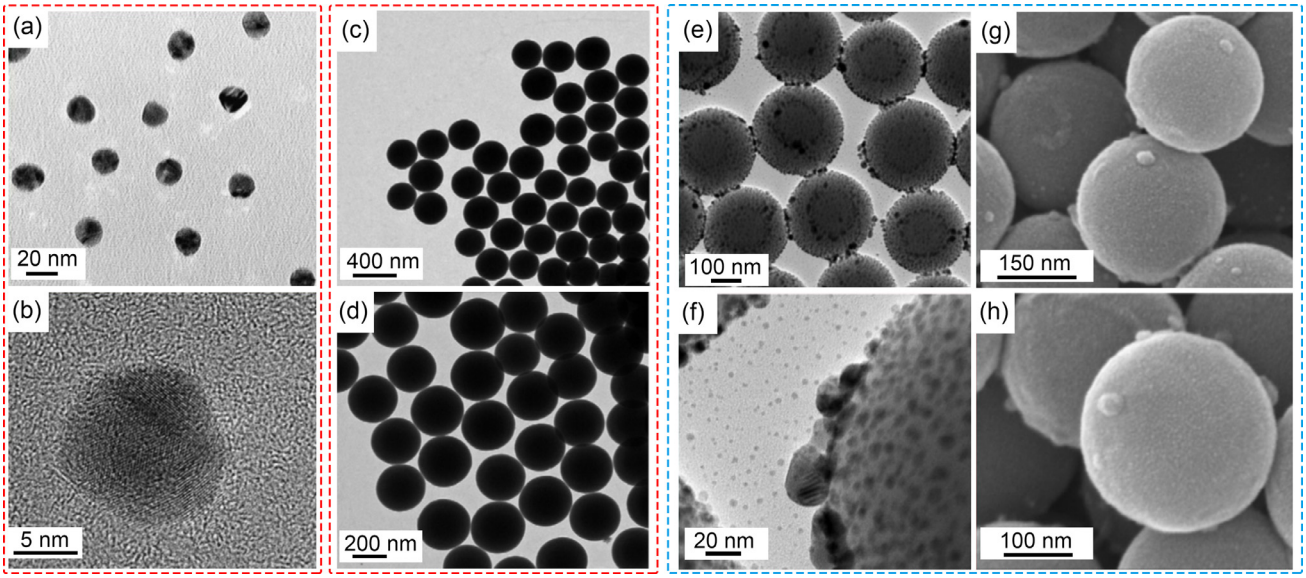

Fig. 6. (a, b) FE-TEM images of PVP-stabilized Ag NPs; (c, d) FE-TEM images of SiO_2 NPs; (e, f) FE-TEM images of Ag-SiO_2 NPs; (g, h) FE-SEM images of Ag-SiO_2 NPs [204]. (Reprinted from *Colloids Surf. Physicochem. Eng. Aspects*, 275(1-3), S.-D. Oh; S. Lee; S.-H. Choi; I.-S. Lee; Y.-M. Lee; J.-H. Chun; H.-J. Park, Synthesis of Ag and Ag–SiO2 nanoparticles by γ-irradiation and their antibacterial and antifungal efficiency against Salmonella enterica serovar Typhimurium and Botrytis cinerea, 228-233, Copyright (2006), with permission from Elsevier).

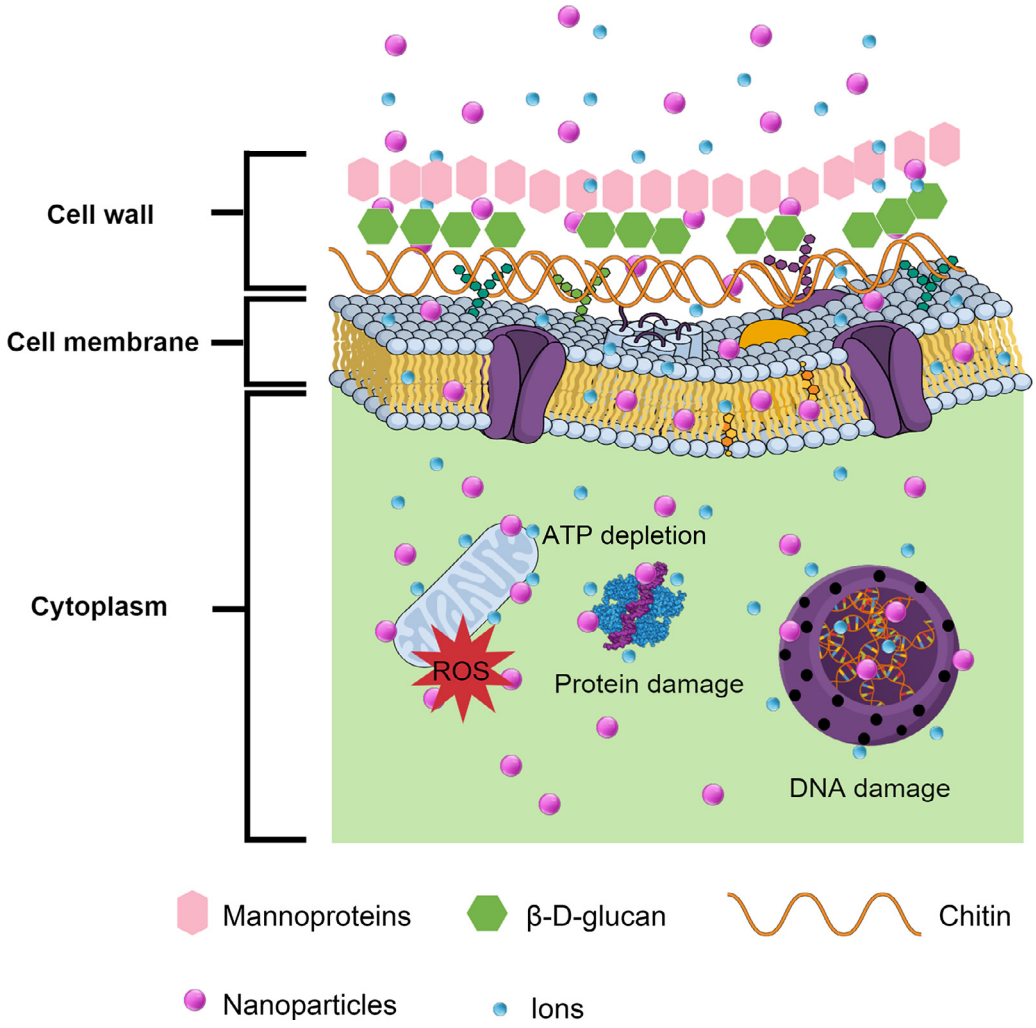

Fig. 7. Schematic showing some of the possible antifungal mechanisms of inorganic NPs. Inorganic NPs could adsorb on the surface of fungal cells and then enter the cell by transportation or endocytosis. Once inorganic NPs are in contact with the cytoplasm, they can affect the function of mitochondria and promote the production of ROS [216]. ROS and ions released from inorganic NPs may trigger irreversible biological damage and alterations in some key genes' expression levels [54,79,88,93,216,218–224]. The schematic illustration is created using Mind the Graph.

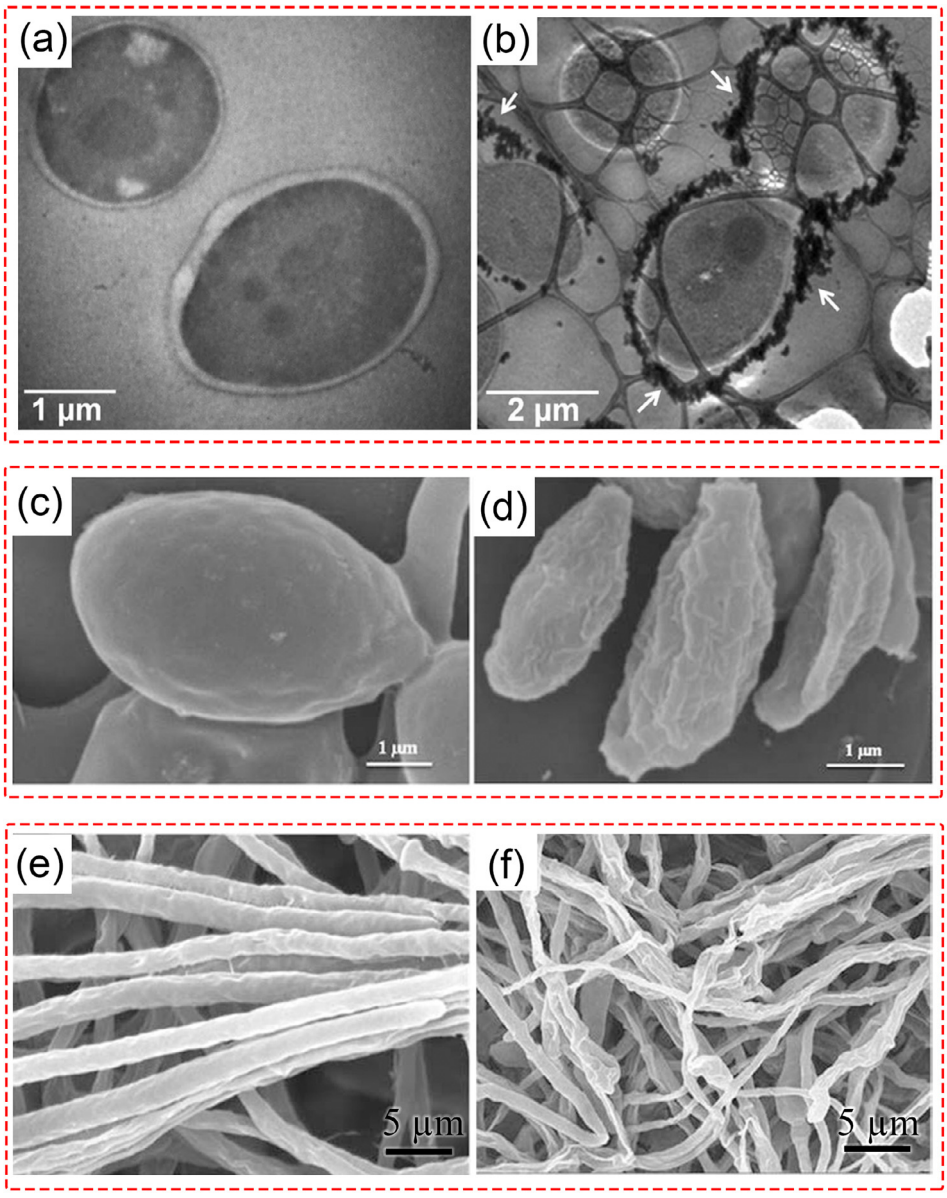

Fig. 8. TEM images of *Candida albicans* after 24 h treatment without Ag NPs (a) and with Ag NPs at their MIC (b) show that the Ag NPs were agglomerated and surrounded the fungal cells [226]. (Adapted with permission from the authors.) SEM images of spores of powdery mildew after 4 days treatment with water (c) and 50 µg/mL Ag NPs (d) show that the spores treated with Ag NPs were wrinkled and deflated [228]. (Adapted with permission from the authors.) SEM images of hyphae of *Colletotrichum gloeosporioides* after 3 days treatment with water (e) and 100 µg/mL Ag NPs (f) show that the hyphae were clearly damaged after treatment with Ag NPs [231]. (Adapted with permission from the authors.)

albicans [226]. TEM images revealed a high degree of accumulation of Ag NPs around the outside of the cells, as shown in Fig. 8(b). The authors proposed that the Ag NPs used in this study did not penetrate the cells, but instead released Ag^+ ions which infiltrated into the cells and lead to the formation of NPs through chemical reduction by organic compounds present in the cell wall and cytoplasm [226]. Ag NPs were also reported to exert their antifungal activities by inhibiting the conidial germination [93,222], inhibiting the growth of sclerotia and mycelia [77], damaging fungal spores (conidia) (Fig. 8(d)) [227,228] and hyphae (Fig. 8(f)) [222,227–230].

The specific antifungal mechanisms of Au NPs have also recently been proposed in the literature. Au NPs have been shown to be able to easily attach to the surface of microorganisms and cause damage to the cells, with complete destruction of the flagella [232]. Au NPs can also restrict the transmembrane H^+ efflux in fungal cells [114], and inhibit the H^+-ATPase leading to intracellular acidification and cell death [113].

Although the exact underlying antifungal mechanisms of ZnO NPs at the molecular level are yet to be elucidated, there are some reported mechanisms which have also been found in Ag NPs [233]. The antifungal mechanisms of ZnO NPs identified thus far include promoting ROS production [142,234,235], disrupting the fungal cell membrane, resulting in decreases of fungal enzymatic activity [138], inhibiting the conidial development and distorting the conidiophores [132], impairing nucleic acids [132], damaging fungal hyphae [132,143] and conidia [143], inhibiting the spore germination capabilities of the fungi [127], and inducing leakage of proteins from the targeted fungal cells [130]. In addition to these discoveries, light illumination has been shown to further enhance the antifungal activity of ZnO NPs by increasing their promotion of

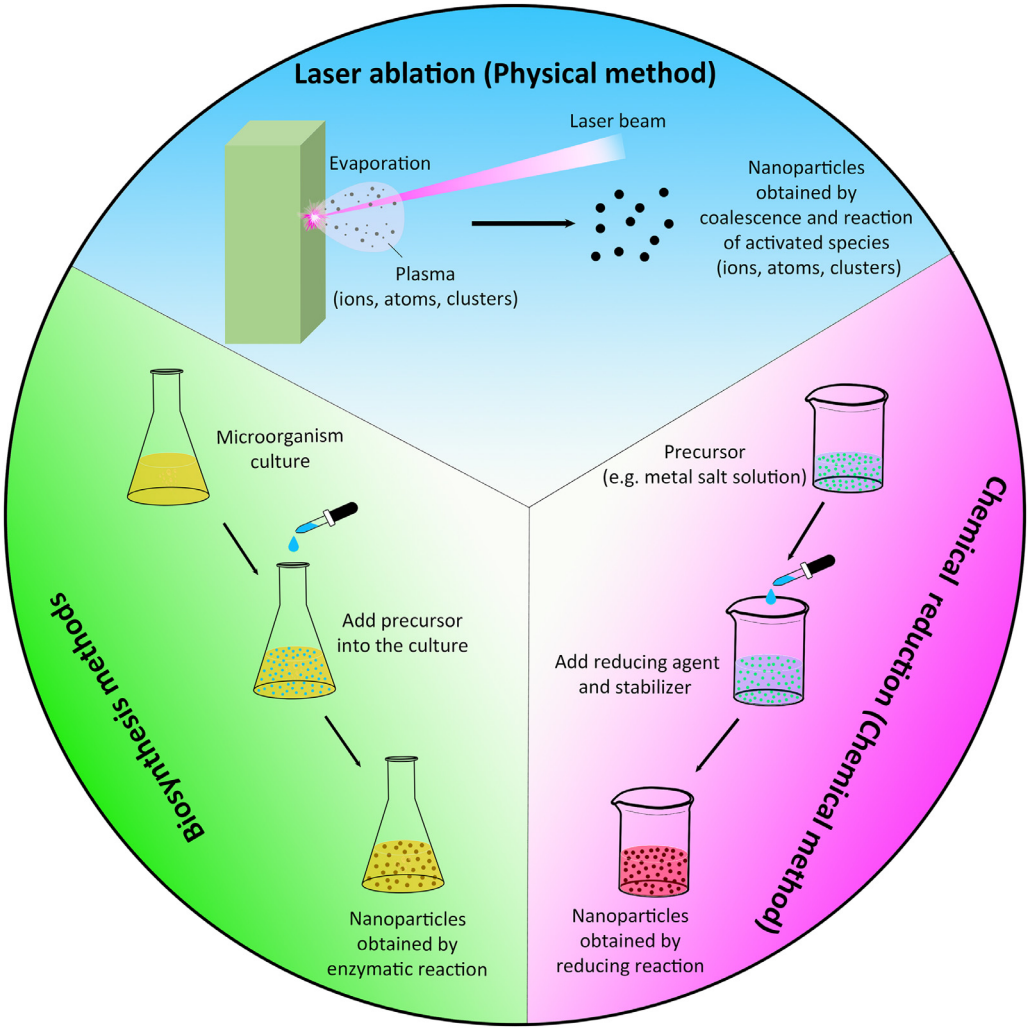

Fig. 9. Illustration of selected typical inorganic nanoparticle fabrication methods. A typical physical method is laser ablation, which focuses a laser beam on a bulk of material immersed in a liquid solution. The mechanism is mainly thermal evaporation, in which plasma and vapor are generated when a focused laser beam heats the bulk material, which then interact with the liquid medium to form nanoparticles through nucleation and growth steps [245]. A typical chemical method is chemical reduction, which uses reducing agents to reduce the ions from precursors into elemental nanoparticles, and stabilizers to stabilize nanoparticles [107,108]. Biosynthesis methods take use of enzymes like nicotinamide adenine dinucleotide-dependent reductase in the microorganisms to convert ions from precursors into elemental nanoparticles [250].

ROS production in fungal cells [139]. Similar to Ag NPs, Zn^{2+} was found to have significant antifungal activity as well [54].

In addition to the specific mechanisms listed above, the attractive antifungal activity of these NPs can also benefit from their characteristic small diameters. With a large surface area to volume ratio, NPs can effectively cover the microorganisms and reduce oxygen supply for respiration, providing another possible method of fungal damage [236].

8. Fabrication methods of antifungal inorganic nanoparticles

Physical, chemical, and biosynthesis methods can be used to prepare inorganic antimicrobial NPs. Physical methods are a bottom-up approach in which nanomaterials are fabricated from bulk materials. It generally involves two basic steps, the evaporation of the bulk material followed by the rapid controlled condensation to produce the required particle size. The material can be vaporized by γ-irradiation [204], laser ablation [168] and high-voltage arc discharge methods [237]. Chemical methods generally take use of various chemical reactions to convert high-valence states of elements to zero-valence nanoparticles. Chemical methods include acid decomposition [238], chemical precipitation [198,239], sonochemical methods [66], sol-gel methods [240,241], chemical reduction [107,114,139,242], and catalytic reduction [243], solvothermal synthesis [244] and thermal decomposition [245], among which the chemical reduction technique is the most commonly used. Biosynthesis involves microorganisms capturing target ions from the environment and then converting the ions into elemental nanoparticles by enzymatic reactions [246].

Nanoparticles in solution generally represent a relatively unstable colloidal system because nanoparticles tend to aggregate to reduce their high surface energy [247]. Due to the short distance between nanoparticles, adjacent nanoparticles are easily attracted to each other by van der Waals forces in solution and tend to aggregate [248]. Therefore, providing a stabilizer on their surface that separates nanoparticles from each other is the most common way to improve the stability of nanoparticles [249]. A wide range of polymers or surfactants can be used as stabilizers for NPs, and different stabilizers may give rise to different antifungal efficacies of the resultant NPs. Fig. 9 illustrates selected typical inorganic nanoparticle fabrication methods.

Green synthesis falls under the category of a chemical reduction method. The term green synthesis is generally used to distinguish it from normal chemical reactions mainly because it uses biological

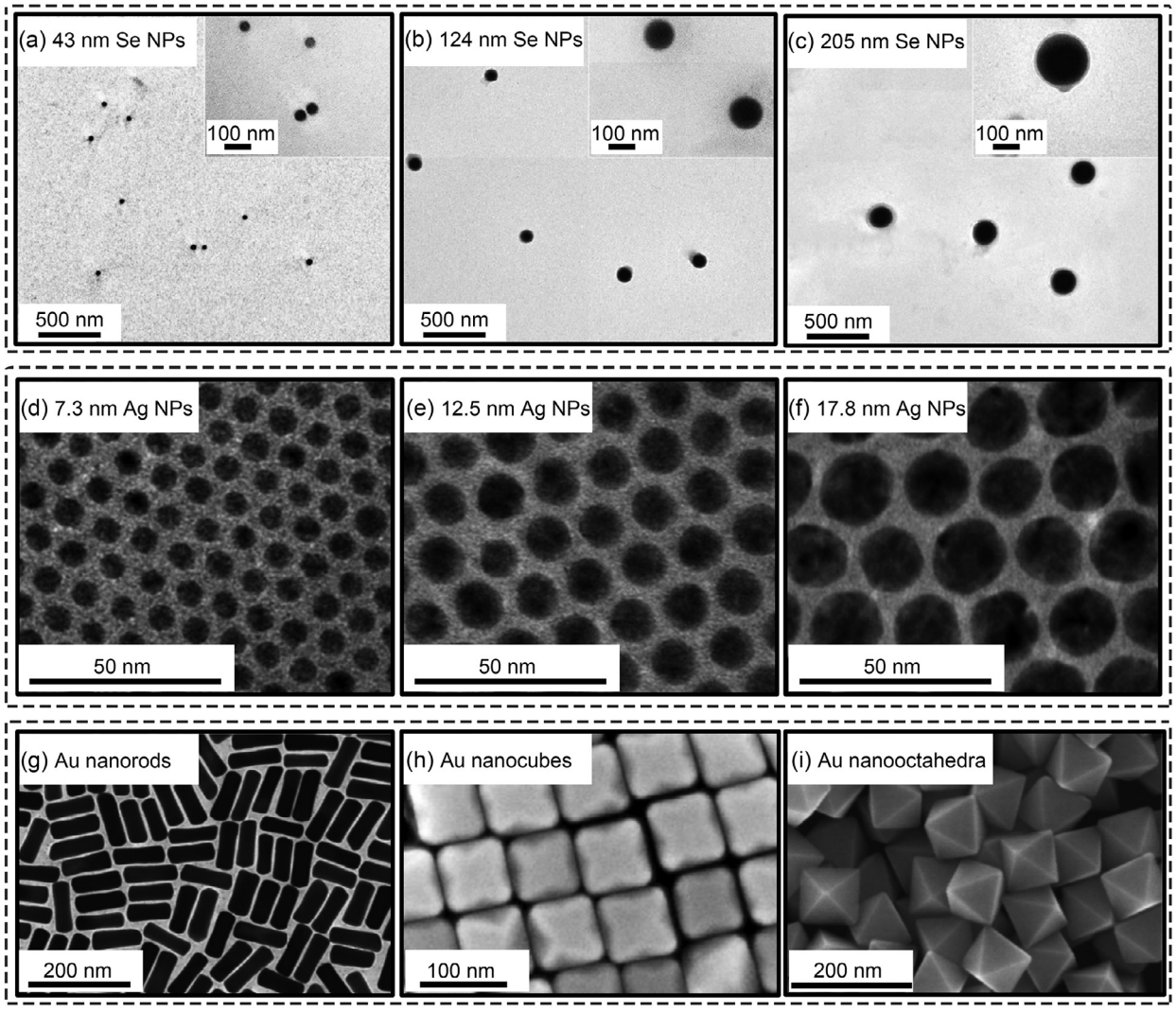

Fig. 10. (a–c) TEM images of Se NPs with different sizes fabricated at various concentrations of reducing agent [166]; (Reproduced from Ref. [161] with permission from the Royal Society of Chemistry.) (d–f) TEM images of Ag NPs with different sizes fabricated at various reaction temperatures [258]; (Adapted from S. Peng, J.M. McMahon, G.C. Schatz, S.K. Gray, Y. Sun, Reversing the size-dependence of surface plasmon resonances, *Proceedings of the National Academy of Sciences*, 2010, 107(33), 14530-14534, with permission from PNAS) (g) Au nanorods [260]; (Reprinted by permission from Springer Nature: Springer, *Nano-Micro Lett*., Angle-resolved plasmonic properties of single gold nanorod dimers, J. Wu; X. Lu; Q. Zhu; J. Zhao; Q. Shen; L. Zhan; W. Ni, Springer(2014).) (h) Au nanocubes [261]; (Reprinted from *Chemical Engineering Journal*, 288, M. Thiele; J. Z. E. Soh; A. Knauer; D. Malsch; O. Stranik; R. Mueller; A. Csaki; T. Henkel; J. M. Koehler; W. Fritzsche, Gold nanocubes–Direct comparison of synthesis approaches reveals the need for a microfluidic synthesis setup for a high reproducibility, 432-440, Copyright (2016), with permission from Elsevier.) (i) Au nanooctahedra [262]. (Adapted with permission from A facile polyol route to uniform gold octahedra with tailorable size and their optical properties. C. Li; K. L. Shuford; M. Chen; E. J. Lee; S. O. Cho. *ACS nano* 2008, 2 (9), 1760-1769. Copyright 2008, American Chemical Society.)

products as reducing agents and stabilizers. These biological products can be further categorized into three classes: plant sources, animal sources, and bacterial and fungal filtrates. The plant sources include leaf extracts [78,95,251], seed extracts [252] and flower extracts [253] from different species of plants, whereas the animal sources include materials such as cow's milk [254]. Green synthesis is a very popular fabrication method for antifungal inorganic nanoparticles in the research literature. The main advantage of using biological products rather than industrial chemicals is their generally mild reaction conditions [255–257]. Many types of NPs could be fabricated using green synthesis methods, including Ag NPs, Au NPs, ZnO NPs, CuO NPs, Se NPs, ZrO_2 NPs, Pt NPs, and so forth [62,109,110,128,169,183,192,196]. However, most of these studies did not address the specific active components of these biologics, and the mechanisms of these reactions are unclear. This tends to make the syntheses poorly controlled. Besides, individual differences among organisms and biological samples lead to differences in the composition of these biological extracts, resulting in poor reproducibility.

Another method, biosynthesis is achieved through enzymatic reactions, as found in cellular metabolism [246]. Several particle types like Se NPs could also be directly fabricated through biometabolism by microorganisms, such as bacteria or fungi [67,82]. Poor reproducibility is also a thorny issue for biosynthesis due to the differences between individual organisms.

As mentioned above, size and shape may influence the antimicrobial activity of nanoparticles by influencing cell uptake and other factors [134,135,139]. Particles of different sizes and shapes can be produced by changing the preparation procedures, such as varying the concentrations or types of reagents, changing the reaction temperature, and altering the addition rate of reagents. For example, different sizes of Se NPs were fabricated by changing the concentration of the reducing agent, with lower concentrations leading to larger Se NPs (Fig. 10(a–c)) [166]. Other studies

have altered other variables to vary the particle size and shape; Peng et al., for example, fabricated different sizes of Ag NPs by keeping the reagent concentrations constant whilst changing the temperature (Fig. 10(d–f)) [258]. The shape of Se NPs was changed to needle-like nanorods via the interaction of the anionic selenium precursors with positively charged chitosan molecules during *in situ* synthesis within porous chitosan scaffolds [259]. Au NPs have historically been fabricated mainly based on the reduction of chloroauric acid in the presence of stabilizing agents. Apart from the conventional colloidal Au NPs with spherical morphologies, methods to generate other shapes of Au NPs have been developed in recent years. The production of non-spherical Au NPs is a rather complex process and requires a multistep synthesis including surface blocking detergents such as cetyltrimethylammonium bromide (CTAB) and cetyltrimethylammonium chloride (CTAC). Gold nanorods, for instance, can be prepared via a seed-mediated growth technique, using CTAB as the stabilizing agent (Fig. 10(g)) [260]. The fabrication of gold nanocubes usually needs three distinct steps: the synthesis step, where the seed particles will be formed initially, followed by two independent growth steps (Fig. 10(h)) [261]. Li et al. reported a one-pot reaction method using chloroauric acid as a gold source, along with liquid polyol as the reducing agent and poly(diallyldimethylammonium chloride) as the surfactant to obtain Au nanooctahedra (Fig. 10(i)) [262]. Smitha et al. synthesized Au NPs using the leaf broth of *Cinnamomum zeylanicum* as the reducing agent [110]. They found that at relatively low concentrations of leaf broth, a mixture of triangular and spherical Au NPs was produced, with a decrease in size detected with an increase in leaf broth concentration, while spherical particles were made almost exclusively at a relatively high concentration of the leaf broth.

Besides, the surface properties, such as surface charge and hydrophobicity, are also important factors which can potentially modulate the nanoparticle-fungi and nanoparticle-cell interactions. The stabilizing agents on NPs can also directly act with cells and fungi [100]. The use of antifungal chemicals to functionalize NPs can create synergistic effects [100]. The surface hydrophobicity can provide a barrier to limit the fungal growth on the surface or in the structure of the materials [263]. Microbes usually have a negative charge cell membrane consisting of lipid layers and peptidoglycan. Hence, the positive net surface charge can enhance the interaction of NPs-microbes. The effect of a positive net charge has been confirmed to be helpful for enhancing the antibacterial activity of NPs [58, 167]. This can also enhance antifungal activity. The surface properties of NPs can be easily modulated through ligand engineering to generate particles with new and emergent properties [264,265]. Therefore, the surface chemical modification of NPs with different chemicals plays a pivotal role in the fabrication of NPs with high antifungal efficacy.

9. Conclusions and potential future directions

In this review, we discussed the development of inorganic nanoparticles as next-generation antifungal agents. Although inorganic NPs in antibacterial applications have been widely explored, research on antifungal inorganic NPs is a relatively new field, as it has just blossomed in the past two decades. The antifungal properties of metallic, metal oxide, transition-metal dichalcogenide, and non-metallic nanoparticle systems have been illustrated. Additionally, these particles exhibit a wide range of antifungal mechanisms including release of mycotoxic ions, damage to the membrane or other critical cellular components, ROS production, and ATP depletion.

Among the particles that have been explored for antifungal applications, Ag NPs are the most researched, followed by ZnO NPs. Many reports confirmed that Ag NPs can have effective antifungal activity with suitable fabrication procedures, and Ag NPs were found to have higher antifungal efficacy than most other types of nanoparticles, such as Au NPs, Cu NPs, ZnO NPs, and Se NPs [84,90,227,266,267]. However, Ag NPs also exhibited higher toxicity to mammalian cells and tissues, with relatively low IC_{50} values towards many different types of mammalian cells [95,106]. Ag NPs have also exhibited genotoxicity to human cell lines [268], and induced changes in blood cell counts [269]. Prolonged exposure to soluble silver or uptake of high doses of silver may also induce irreversible pigmentation in the skin (argyria) [270] and cause damage to the kidneys and liver through an increase of inflammatory cytokines [271], potentially limiting their use. The antifungal research results for Au NPs are promising, but the number of studies is small, and more research is needed to thoroughly evaluate the application prospects for Au NPs as antifungal agents. Additionally, gold is not a nutritional element and is highly stable. Long-term use may lead to accumulation in the host's organs and cause harm, so biodistribution studies would also be needed before clinical use could be deemed safe. Cu NPs also showed high antifungal activity, but with relatively high cytotoxicity [272]. TiO_2 NPs need light (ideally ultraviolet) to exert their antifungal activity, which limits their application. Nanomaterials that are less effective against fungi, such as CuO NPs, Fe_3O_4 NPs, S NPs and Te NPs, need doses of hundreds to thousands (or even more) micrograms per millilitre to exert sufficient antifungal activity [161,191]. At such high concentrations, their acute and long-term toxicity to tissues would be a huge barrier to their use. Systematic research on the biodistribution and potential toxicity of antifungal nanoparticles at their effective concentrations is crucial, but the reports on this are very limited so far. Additionally, *in vivo* tests must be considered to further validate the safety of clinically applying these NPs as antifungal treatments. More research assessing the possible negative effects of these nanoparticles in detail will be required to find suitable synthesis and modification methods which can broaden their therapeutic windows.

The NPs made of nutritional elements for humans and animals, such as ZnO, Se and MgO, are promising in antifungal applications as they might function as a nutritional supplement and allow higher doses without toxicity. However, these types of inorganic NPs show much lower antifungal activity compared to Ag NPs, so there is a distinct trade-off. The effect of a positive net charge has been confirmed to be helpful for enhancing the antibacterial activity of NPs. [163] This can also enhance antifungal activity. For example, positively charged chitosan particles also showed good antifungal activity, and their positive charge was considered to interact with negatively charged phospholipid components of fungi membrane [273]. As mentioned above, the antifungal activity of NPs is generally affected by particle size as well. Therefore, finding the optimal particle size to get the highest antifungal efficacy and making NPs with positive net charges might also be a feasible way to enhance the antifungal activity of the NPs discussed in this review. However, the smaller sizes and positive net charges may also lead to higher toxicity towards mammalian cells.

Besides, taking advantage of synergistic fungicidal effects of antifungal drugs with inorganic NPs is a simple and effective way to reduce the dosage of both NPs and antifungal drugs, thereby reducing the toxicity caused by NPs and antifungal drugs. Simultaneously, the combination of the attacking targets of antifungal drugs and NPs has the potential to improve the antimicrobial efficiency, broaden the antifungal spectrum, and reduce the risk of fungal resistance.

Despite the potential of inorganic nanoparticles as antifungal agents, significant research is required before these materials can achieve their maximum clinical impact. First, many of the existing studies have significant limitations. For instance, many studies only qualitatively analyse the antifungal properties of inorganic NPs us-

ing agar diffusion methods, and this lack of quantitative fungicidal data limits comparisons between different particle types and the conclusions that can be drawn. Moreover, many of the quantitative results are not implemented in accordance with unified standards, further hindering the comparison of results between different studies. The Clinical and Laboratory Standards Institute (CLSI) has developed and published reference methods for antifungal susceptibility testing of both yeasts and filamentous fungi [274]. We recommend that these methods or other standardized quantitative studies are done in the future to help develop a more comprehensive and in-depth understanding of the factors that dictate the antifungal efficacy of inorganic NPs.

A second major limitation with many studies is the lack of cytotoxicity testing towards human cell types. This is a critical gap in the research because a clear therapeutic window must be illustrated before these nanoparticles can achieve clinical use. This is especially true for antifungal nanoparticles because fungi and mammalian cells have many similar structures and cellular organelles, given they are both eukaryotic. Thus, the antifungal agents have high chance of showing toxicity towards mammalian cells as well. In future research, we recommend that all newly developed antifungal particles are also assessed for cytotoxicity with relevant human cell types using standardized and quantitative methods.

The use of nanomaterials as next generation antifungal agents is still in its nascency, and we propose several key areas of research that could lead to significant advances in the field. To date, most of the antifungal mechanisms that have been explored are based on established antibacterial mechanisms. Using antimicrobial mechanisms that simultaneously inhibit or kill both bacteria and fungi would be valuable to address polymicrobial infections. However, given that the structures and behaviours of fungal cells are distinctly different from those of bacterial cells, there may be some specific antifungal mechanisms correlated to the biological structures of fungi yet to be elucidated which provide new avenues for optimisation of antifungal performance (e.g., sulphur metabolism). This is particularly important because the antifungal activity of inorganic NPs is generally significantly lower than their antibacterial activity. Improving our understanding and potentially unveiling undiscovered antifungal mechanisms may provide avenues for the design of the next generation of antifungal agents in the future. Besides, designing nanoparticles that can act on distinct targets of fungal cells rather than mammalian cells will be crucial for reducing the cytotoxicity of antifungal nanoparticles. There are several structural differences between fungi and mammalian cells. For instance, fungal cells have outer cell walls that do not present in mammalian cells. Hence, some components in the outer cell wall can be recognised as fungal specific targets. Furthermore, fungal cells have different lipid components in their membranes from mammalian cells, such as ergosterol. Although there are antifungal agents that specifically act on ergosterol currently available, inorganic nanoparticles designed with antifungal mechanisms against fungal specific targets have not yet been reported, to the authors' knowledge. There is a need to design future antifungal inorganic nanomaterials to act on fungi-specific targets, such as via surface chemical modification of nanoparticles to carry molecules that can bind to specific targets. The discovery of more specific fungal targets would also aid in the design of future antifungal agents and would also make it easier to prepare nanoparticles with multiple mechanisms of antifungal action, thereby slowing down the development of resistance to these materials.

Furthermore, many NPs used in the antifungal studies reported to date have been produced by green synthesis methods, which use biological extracts as reducing agents and stabilizers. The reproducibility of these NPs tends to be poor because of the diversity of individual organisms and resulting reagents. Additionally, the specific active chemicals involved in the reactions remain unknown, and the compounds coating the NPs are uncertain. This makes it difficult to assess the influence of these chemicals on the NPs' antifungal performance and their consequential antifungal mechanisms. Future research should seek to clarify the identity of the chemicals coated on the surface of antifungal NPs to improve understanding of which chemicals or chemical properties have a beneficial effect on the antifungal ability and cytotoxicity of these NPs to guide the preparation of safer and more effective antifungal particles in the future.

To sum up, antifungal research on inorganic nanoparticles is still at a very early stage. There remains a pressing need and significant opportunity for further research to explore more effective antifungal inorganic nanomaterial design strategies which optimise performance and safety for future human and animal health treatments. More research needs to be done in the future using standardized testing methods to provide quantitative antifungal assessments of inorganic NPs that can be meaningfully compared. Specific material compositions and properties of the antifungal NPs developed should be clarified, and their antifungal mechanisms should be explored to guide future design improvements. These steps will move the field towards a more comprehensive understanding of the antifungal capabilities of nanoparticles and the most promising directions for enhancing their performance. Critically, *in vitro* and *in vivo* biosafety evaluations on any NPs considered for future human or animal applications need to be conducted to determine their safe therapeutic windows and progress these promising materials to provide commercial and clinical impact.

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.

Acknowledgements

The Australian Research Council (ARC) are thanked for financial support over many years for nanomaterials in the authors' laboratories. A.J.O. and N.M.O.-S. are the recipients of ARC funding (DP201102781) which supported this work. M.M. and X.L. are both supported by the University of Melbourne and an Australian Government Research Training Program Scholarship (Melbourne International Research Scholarship).

References

[1] F.M. Garibotto, A.D. Garro, M.F. Masman, A.M. Rodríguez, P.G. Luiten, M. Raimondi, S.A. Zacchino, C. Somlai, B. Penke, R.D. Enriz, New small-size peptides possessing antifungal activity, Bioorg. Med. Chem. 18 (1) (2010) 158–167.
[2] M.L. Salas, J. Mounier, F. Valence, M. Coton, A. Thierry, E. Coton, Antifungal microbial agents for food biopreservation-a review, Microorganisms 5 (3) (2017) 37.
[3] M.K. Kathiravan, A.B. Salake, A.S. Chothe, P.B. Dudhe, R.P. Watode, M.S. Mukta, S. Gadhwe, The biology and chemistry of antifungal agents: a review, Bioorg. Med. Chem. 20 (19) (2012) 5678–5698.
[4] T.B. Tufa, D.W. Denning, The burden of fungal infections in Ethiopia, J. Fungi 5 (4) (2019) 109.
[5] G.D. Brown, D.W. Denning, N.A. Gow, S.M. Levitz, M.G. Netea, T.C. White, Hidden killers: human fungal infections, Sci. Transl. Med. 4 (165) (2012) 165rv13 -165rv13.
[6] D.W. Denning, W.W. Hope, Therapy for fungal diseases: opportunities and priorities, Trends Microbiol. 18 (5) (2010) 195–204.
[7] M.D. Richardson, Opportunistic and pathogenic fungi, J. Antimicrob. Chemother. 28 (suppl_A) (1991) 1–11.
[8] A. León-Buitimea, J.A. Garza-Cervantes, D.Y. Gallegos-Alvarado, M. Osorio–Concepción, J.R. Morones-Ramírez, Nanomaterial-based antifungal therapies to combat fungal diseases aspergillosis, Coccidioidomycosis, Mucormycosis, and candidiasis, Pathogens 10 (10) (2021) 1303.
[9] T. Patterson, Treatment and prevention of fungal infections, Focus on candidemia. New York: Applied Clinical Education 23 (2007) 7-80.

[10] M. Tampieri, Update on the diagnosis of dermatomycosis, Parassitologia 46 (1-2) (2004) 183–186.
[11] M.C. Fisher, N.J. Hawkins, D. Sanglard, S.J. Gurr, Worldwide emergence of resistance to antifungal drugs challenges human health and food security, Science 360 (6390) (2018) 739–742.
[12] R. Raliya, T. Singh Chadha, K. Haddad, P. Biswas, Perspective on nanoparticle technology for biomedical use, Curr. Pharm. Des. 22 (17) (2016) 2481–2490.
[13] K. McNamara, S.A. Tofail, Nanoparticles in biomedical applications, Adv. Phys. X 2 (1) (2017) 54–88.
[14] P. Vandeputte, S. Ferrari, A.T. Coste, Antifungal resistance and new strategies to control fungal infections, Int. J. Microbiol. 2012 (2012) 713687.
[15] J.J. Worrall, in: Brief Introduction to Fungi, Structure and Dynamics of Fungal Populations, Springer, 1999, pp. 1–18.
[16] J. Webster, R. Weber, Introduction to Fungi, Cambridge University Press, 2007.
[17] T. Di Mambro, I. Guerriero, L. Aurisicchio, M. Magnani, E. Marra, The Yin and Yang of current antifungal therapeutic strategies: how can we harness our natural defenses? Front. Pharmacol. 10 (2019) 80.
[18] S.G. Martin, R.A. Arkowitz, Cell polarization in budding and fission yeasts, FEMS Microbiol. Rev. 38 (2) (2014) 228–253.
[19] T.K Mazu, B.A Bricker, H. Flores-Rozas, S.Y. Ablordeppey, The mechanistic targets of antifungal agents: an overview, Mini Rev. Med. Chem. 16 (7) (2016) 555–578.
[20] S.M. Bowman, S.J. Free, The structure and synthesis of the fungal cell wall, Bioessays 28 (8) (2006) 799–808.
[21] J.D. Weete, Structure and function of sterols in fungi, in: Advances in Lipid Research, Elsevier, 1989, pp. 115–167.
[22] C. Giles, S.J. Lamont-Friedrich, T.D. Michl, H.J. Griesser, B.R. Coad, The importance of fungal pathogens and antifungal coatings in medical device infections, Biotechnol. Adv. 36 (1) (2018) 264–280.
[23] S.Y. Ablordeppey, P. Fan, J.H. Ablordeppey, L. Mardenborough, Systemic antifungal agents against AIDS-related opportunistic infections: current status and emerging drugs in development, Curr. Med. Chem. 6 (12) (1999) 1151–1196.
[24] B.P. Mathew, M. Nath, Recent approaches to antifungal therapy for invasive mycoses, ChemMedChem Chem. Enabling Drug Discov. 4 (3) (2009) 310–323.
[25] M. Bard, N. Lees, T. Turi, D. Craft, L. Cofrin, R. Barbuch, C. Koegel, J. Loper, Sterol synthesis and viability oferg11 (cytochrome P450 lanosterol demethylase) mutations inSaccharomyces cerevisiae andCandida albicans, Lipids 28 (11) (1993) 963–967.
[26] L. Alcazar-Fuoli, E. Mellado, Ergosterol biosynthesis in Aspergillus fumigatus: its relevance as an antifungal target and role in antifungal drug resistance, Front. Microbiol. 3 (2013) 439.
[27] K. Hatano, Y. Morishita, T. Nakai, F. Ikeda, Antifungal mechanism of FK463 against Candida albicans and Aspergillus fumigatus, J. Antibiot. 55 (2) (2002) 219–222.
[28] Y. Chen, H. Zeng, J. Tian, X. Ban, B. Ma, Y. Wang, Antifungal mechanism of essential oil from Anethum graveolens seeds against Candida albicans, J. Med. Microbiol. 62 (8) (2013) 1175–1183.
[29] H.A. Krebs, D. Wiggins, M. Stubbs, A. Sols, F. Bedoya, Studies on the mechanism of the antifungal action of benzoate, Biochem. J. 214 (3) (1983) 657–663.
[30] J. Amich, Sulfur metabolism as a promising source of new antifungal targets, J. Fungi 8 (3) (2022) 295.
[31] F.C. Odds, A.J. Brown, N.A. Gow, Antifungal agents: mechanisms of action, Trends Microbiol. 11 (6) (2003) 272–279.
[32] D.G. Lee, Y. Park, H.N. Kim, H.K. Kim, P.I. Kim, B.H. Choi, K.S. Hahm, Antifungal mechanism of an antimicrobial peptide, HP (2–20), derived from N-terminus of Helicobacter pylori ribosomal protein L1 against Candida albicans, Biochem. Biophys. Res. Commun. 291 (4) (2002) 1006–1013.
[33] N. Komaki, T. Watanabe, A. Ogasawara, N. Sato, T. Mikami, T. Matsumoto, Antifungal mechanism of hinokitiol against Candida albicans, Biol. Pharm. Bull. 31 (4) (2008) 735–737.
[34] A.C. Mesa-Arango, L. Scorzoni, O. Zaragoza, It only takes one to do many jobs: Amphotericin B as antifungal and immunomodulatory drug, Front. Microbiol. 3 (2012) 286.
[35] A.C. Mesa-Arango, N. Trevijano-Contador, E. Román, R. Sánchez-Fresneda, C. Casas, E. Herrero, J.C. Argüelles, J. Pla, M. Cuenca-Estrella, O. Zaragoza, The production of reactive oxygen species is a universal action mechanism of amphotericin B against pathogenic yeasts and contributes to the fungicidal effect of this drug, Antimicrob. Agents Chemother. 58 (11) (2014) 6627–6638.
[36] R.K. Tripathi, D. Gottlieb, Mechanism of action of the antifungal antibiotic pyrrolnitrin, J. Bacteriol. 100 (1) (1969) 310–318.
[37] Y. Elad, H. Yunis, T. Katan, Multiple fungicide resistance to benzimidazoles, dicarboximides and diethofencarb in field isolates of Botrytis cinerea in Israel, Plant Pathol. 41 (1) (1992) 41–46.
[38] J. Van der Linden, M. Arendrup, A. Warris, K. Lagrou, H. Pelloux, P. Hauser, E. Chryssanthou, E. Mellado, S. Kidd, A. Tortorano, Prospective multicenter international surveillance of azole resistance in Aspergillus fumigatus, Emerg. Infect. Dis. 21 (6) (2015) 1041.
[39] M. Sanguinetti, B. Posteraro, C. Lass-Flörl, Antifungal drug resistance among Candida species: mechanisms and clinical impact, Mycoses 58 (2015) 2–13.
[40] S. Vallabhaneni, A.A. Cleveland, M.M. Farley, L.H. Harrison, W. Schaffner, Z.G. Beldavs, G. Derado, C.D. Pham, S.R. Lockhart, R.M. Smith, Epidemiology and Risk Factors for Echinocandin Nonsusceptible Candida glabrata Bloodstream Infections: Data from a Large Multisite Population-Based Candidemia Surveillance Program, 2008–2014, Open Forum Infectious Diseases, Oxford University Press, 2015.
[41] B.D. Alexander, M.D. Johnson, C.D. Pfeiffer, C. Jiménez-Ortigosa, J. Catania, R. Booker, M. Castanheira, S.A. Messer, D.S. Perlin, M.A. Pfaller, Increasing echinocandin resistance in Candida glabrata: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations, Clin. Infect. Dis. 56 (12) (2013) 1724–1732.
[42] D. Farmakiotis, J.J. Tarrand, D.P. Kontoyiannis, Drug-resistant Candida glabrata infection in cancer patients, Emerg. Infect. Dis. 20 (11) (2014) 1833.
[43] J.L. Xu, Y.X. Luo, S.H. Yuan, L.W. Li, N.N. Liu, Antifungal nanomaterials: current progress and future directions, Innov. Digit. Health Diagn. Biomark. 1 (1) (2021) 3–7.
[44] N.M. Revie, K.R. Iyer, N. Robbins, L.E. Cowen, Antifungal drug resistance: evolution, mechanisms and impact, Curr. Opin. Microbiol. 45 (2018) 70–76.
[45] M.W. Hokken, B. Zwaan, W. Melchers, P. Verweij, Facilitators of adaptation and antifungal resistance mechanisms in clinically relevant fungi, Fungal Genet. Biol. 132 (2019) 103254.
[46] H.C. Flemming, J. Wingender, The biofilm matrix, Nat. Rev. Microbiol. 8 (9) (2010) 623–633.
[47] M. Íñigo, J.L. Del Pozo, Fungal biofilms: from bench to bedside, Rev. Esp. Quimioter. 31 (Suppl 1) (2018) 35.
[48] C. Reichhardt, D.A. Stevens, L. Cegelski, Fungal biofilm composition and opportunities in drug discovery, Future Med. Chem. 8 (12) (2016) 1455–1468.
[49] K.F. Mitchell, R. Zarnowski, D.R. Andes, Fungal super glue: the biofilm matrix and its composition, assembly, and functions, PLoS Pathog. 12 (9) (2016) e1005828.
[50] V. Cepas, Y. López, Y. Gabasa, C.B. Martins, J.D. Ferreira, M.J. Correia, L. Santos, F. Oliveira, V. Ramos, M. Reis, Inhibition of bacterial and fungal biofilm formation by 675 extracts from microalgae and cyanobacteria, Antibiotics 8 (2) (2019) 77.
[51] A.S. Lynch, G.T. Robertson, Bacterial and fungal biofilm infections, Annu. Rev. Med. 59 (2008) 415–428.
[52] R.J. McLean, J.S. Lam, L.L. Graham, Training the biofilm generation-a tribute to JW Costerton, J. Bacteriol. 194 (24) (2012) 6706–6711.
[53] R.M. Donlan, J.W. Costerton, Biofilms: survival mechanisms of clinically relevant microorganisms, Clin. Microbiol. Rev. 15 (2) (2002) 167–193.
[54] J. Li, H. Sang, H. Guo, J.T. Popko, L. He, J.C. White, O.P. Dhankher, G. Jung, B. Xing, Antifungal mechanisms of ZnO and Ag nanoparticles to Sclerotinia homoeocarpa, Nanotechnology 28 (15) (2017) 155101.
[55] A.J. Huh, Y.J. Kwon, "Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era, J. Control. Release 156 (2) (2011) 128–145.
[56] N. Padmavathy, R. Vijayaraghavan, Enhanced bioactivity of ZnO nanoparticles—an antimicrobial study, Sci. Technol. Adv. Mater. 9 (3) (2008) 035004.
[57] T. Begum, P.A. Follett, J. Mahmud, L. Moskovchenko, S. Salmieri, Z. Allahdad, M. Lacroix, Silver nanoparticles-essential oils combined treatments to enhance the antibacterial and antifungal properties against foodborne pathogens and spoilage microorganisms, Microb. Pathog. 164 (2022) 105411.
[58] T. Huang, J.A. Holden, E.C. Reynolds, D.E. Heath, N.M. O'Brien-Simpson, A.J. O'Connor, Multifunctional antimicrobial polypeptide-selenium nanoparticles combat drug-resistant bacteria, ACS Appl. Mater. Interfaces 12 (50) (2020) 55696–55709.
[59] D. Chao, Q. Dong, J. Chen, Z. Yu, W. Wu, Y. Fang, L. Liu, S. Dong, Highly efficient disinfection based on multiple enzyme-like activities of Cu3P nanoparticles: a catalytic approach to impede antibiotic resistance, Appl. Catal. B 304 (2022) 121017.
[60] S. Qayyum, A.U. Khan, Nanoparticles vs. biofilms: a battle against another paradigm of antibiotic resistance, MedChemComm 7 (8) (2016) 1479–1498.
[61] M.M. Hassan, Antibacterial and antifungal thioglycolic acid-capped silver nanoparticles and their application on wool fabric as a durable antimicrobial treatment, ChemistrySelect 2 (1) (2017) 504–512.
[62] C. Jayaseelan, R. Ramkumar, A.A. Rahuman, P. Perumal, Green synthesis of gold nanoparticles using seed aqueous extract of Abelmoschus esculentus and its antifungal activity, Ind. Crops Prod. 45 (2013) 423–429.
[63] M.F. Waxman, The Agrochemical and Pesticides Safety Handbook, CRC Press, 1998.
[64] Y. Wei, S. Chen, B. Kowalczyk, S. Huda, T.P. Gray, B.A. Grzybowski, Synthesis of stable, low-dispersity copper nanoparticles and nanorods and their antifungal and catalytic properties, J. Phys. Chem. C 114 (37) (2010) 15612–15616.
[65] K. Mukherjee, K. Acharya, A. Biswas, N.R. Jana, TiO_2 nanoparticles co-doped with nitrogen and fluorine as visible-light-activated antifungal agents, ACS Appl. Nano Mater. 3 (2) (2020) 2016–2025.
[66] M. Rastgoo, M. Montazer, R.M. Malek, T. Harifi, M.M. Rad, Ultrasound mediation for one-pot sonosynthesis and deposition of magnetite nanoparticles on cotton/polyester fabric as a novel magnetic, photocatalytic, sonocatalytic, antibacterial and antifungal textile, Ultrason. Sonochem. 31 (2016) 257–266.
[67] Z.B. Kazempour, M.H. Yazdi, F. Rafii, A.R. Shahverdi, Sub-inhibitory concentration of biogenic selenium nanoparticles lacks post antifungal effect for Aspergillus niger and Candida albicans and stimulates the growth of Aspergillus niger, Iran. J. Microbiol. 5 (1) (2013) 81.
[68] B. Zare, Z. Sepehrizadeh, M.A. Faramarzi, M. Soltany-Rezaee-Rad, S. Rezaie, A.R. Shahverdi, Antifungal activity of biogenic tellurium nanoparticles against C andida albicans and its effects on squalene monooxygenase gene expression, Biotechnol. Appl. Biochem. 61 (4) (2014) 395–400.
[69] M. Rai, K. Kon, A. Ingle, N. Duran, S. Galdiero, M. Galdiero, Broad-spectrum bioactivities of silver nanoparticles: the emerging trends and future prospects, Appl. Microbiol. Biotechnol. 98 (5) (2014) 1951–1961.

[70] X. Li, T. Huang, D.E. Heath, N.M. O'Brien-Simpson, A.J. O'Connor, Antimicrobial nanoparticle coatings for medical implants: design challenges and prospects, Biointerphases 15 (6) (2020) 060801.
[71] L. Pereira, N. Dias, J. Carvalho, S. Fernandes, C. Santos, N. Lima, Synthesis, characterization and antifungal activity of chemically and fungal-produced silver nanoparticles against T richophyton rubrum, J. Appl. Microbiol. 117 (6) (2014) 1601–1613.
[72] Y.K. Jo, B.H. Kim, G. Jung, Antifungal activity of silver ions and nanoparticles on phytopathogenic fungi, Plant Dis. 93 (10) (2009) 1037–1043.
[73] L. Zhou, X. Zhao, M. Li, Y. Lu, C. Ai, C. Jiang, Y. Liu, Z. Pan, J. Shi, Antifungal activity of silver nanoparticles synthesized by iturin against Candida albicans *in vitro* and *in vivo*, Appl. Microbiol. Biotechnol. 105 (9) (2021) 3759–3770.
[74] M.A. Malik, M.G. Batterjee, M.R. Kamli, K.A. Alzahrani, E.Y. Danish, A. Nabi, Polyphenol-capped biogenic synthesis of noble metallic silver nanoparticles for antifungal activity against Candida auris, J. Fungi 8 (6) (2022) 639.
[75] R. Anitha, B. Karthikeyan, T. Pandiyarajan, S. Vignesh, R.A. James, K. Vishwanathan, B. Murari, Antifungal studies on biocompatible polymer encapsulated silver nanoparticles, Int. J. Nanosci. 10 (04n05) (2011) 1179–1183.
[76] A. Ogar, G. Tylko, K. Turnau, Antifungal properties of silver nanoparticles against indoor mould growth, Sci. Total Environ. 521 (2015) 305–314.
[77] M.S. Nejad, G.H.S. Bonjar, M. Khatami, A. Amini, S. Aghighi, *In vitro* and *in vivo* antifungal properties of silver nanoparticles against Rhizoctonia solani, a common agent of rice sheath blight disease, IET Nanobiotechnol. 11 (3) (2016) 236–240.
[78] A.H.A. Kelkawi, A.A. Kajani, A.K. Bordbar, Green synthesis of silver nanoparticles using Mentha pulegium and investigation of their antibacterial, antifungal and anticancer activity, IET Nanobiotechnol. 11 (4) (2016) 370–376.
[79] A.H. Atef, K.M. Mogda, H. Mahmoudc, Biosynthesis of silver nanoparticles (AgNps)(a model of metals) by Candida albicans and its antifungal activity on some fungal pathogens (Trichophyton mentagrophytes and Candida albicans), NY Sci. J. 6 (3) (2013) 27–43.
[80] R. Bryaskova, D. Pencheva, S. Nikolov, T. Kantardjiev, Synthesis and comparative study on the antimicrobial activity of hybrid materials based on silver nanoparticles (AgNps) stabilized by polyvinylpyrrolidone (PVP), J. Chem. Biol. 4 (4) (2011) 185.
[81] Y. Qian, H. Yu, D. He, H. Yang, W. Wang, X. Wan, L. Wang, Biosynthesis of silver nanoparticles by the endophytic fungus Epicoccum nigrum and their activity against pathogenic fungi, Bioprocess Biosyst. Eng. 36 (11) (2013) 1613–1619.
[82] B. Xue, D. He, S. Gao, D. Wang, K. Yokoyama, L. Wang, Biosynthesis of silver nanoparticles by the fungus Arthroderma fulvum and its antifungal activity against genera of Candida, Aspergillus and Fusarium, Int. J. Nanomed. 11 (2016) 1899.
[83] F. Martinez-Gutierrez, P.L. Olive, A. Banuelos, E. Orrantia, N. Nino, E.M. Sanchez, F. Ruiz, H. Bach, Y. Av-Gay, Synthesis, characterization, and evaluation of antimicrobial and cytotoxic effect of silver and titanium nanoparticles, Nanomed. Nanotechnol. Biol. Med. 6 (5) (2010) 681–688.
[84] C. Ashajyothi, C. Prabhurajeshwar, H.K. Handral, C. Kelmani, Investigation of antifungal and anti-mycelium activities using biogenic nanoparticles: an eco-friendly approach, Environ. Nanotechnol. Monit. Manag. 5 (2016) 81–87.
[85] D. Monteiro, L. Gorup, S. Silva, M. Negri, E. De Camargo, R. Oliveira, D.D.B. Barbosa, M. Henriques, Silver colloidal nanoparticles: antifungal effect against adhered cells and biofilms of Candida albicans and Candida glabrata, Biofouling 27 (7) (2011) 711–719.
[86] K.B. Narayanan, H.H. Park, Unnatural amino acid-mediated synthesis of silver nanoparticles and their antifungal activity against Candida species, J. Nanopart. Res. 16 (8) (2014) 2523.
[87] A. Panáček, M. Kolář, R. Večeřová, R. Prucek, J. Soukupova, V. Kryštof, P. Hamal, R. Zbořil, L. Kvítek, Antifungal activity of silver nanoparticles against Candida spp, Biomaterials 30 (31) (2009) 6333–6340.
[88] K. Ishida, T.F. Cipriano, G.M. Rocha, G. Weissmüller, F. Gomes, K. Miranda, S. Rozental, Silver nanoparticle production by the fungus Fusarium oxysporum: nanoparticle characterisation and analysis of antifungal activity against pathogenic yeasts, Mem. Inst. Oswaldo Cruz 109 (2) (2014) 220–228.
[89] C.Y. San, M.M. Don, Biosynthesis of silver nanoparticles from Schizophyllum commune and *in-vitro* antibacterial and antifungal activity studies, J. Phys. Sci. 24 (2) (2013) 83.
[90] C.E. Peña-González, E. Pedziwiatr-Werbicka, T. Martín-Pérez, E.M. Szewczyk, J.L. Copa-Patiño, J. Soliveri, J. Pérez-Serrano, R. Gómez, M. Bryszewska, J. Sánchez-Nieves, Antibacterial and antifungal properties of dendronized silver and gold nanoparticles with cationic carbosilane dendrons, Int. J. Pharm. 528 (1-2) (2017) 55–61.
[91] D. Monteiro, S. Silva, M. Negri, L. Gorup, E. De Camargo, R. Oliveira, D.d.B. Barbosa, M. Henriques, Silver nanoparticles: influence of stabilizing agent and diameter on antifungal activity against Candida albicans and Candida glabrata biofilms, Lett. Appl. Microbiol. 54 (5) (2012) 383–391.
[92] S.A. Al-thabaiti, Z. Khan, N. Manzoor, Biosynthesis of silver nanoparticles and its antibacterial and antifungal activities towards Gram-positive, Gram-negative bacterial strains and different species of Candida fungus, Bioprocess Biosyst. Eng. 38 (9) (2015) 1773–1781.
[93] K.J. Kim, W.S. Sung, B.K. Suh, S.K. Moon, J.S. Choi, J.G. Kim, D.G. Lee, Antifungal activity and mode of action of silver nano-particles on Candida albicans, Biometals 22 (2) (2009) 235–242.
[94] S.A.A. Mousavi, S. Salari, S. Hadizadeh, Evaluation of antifungal effect of silver nanoparticles against Microsporum canis, Trichophyton mentagrophytes and Microsporum gypseum, Iran. J. Biotechnol. 13 (4) (2015) 38.
[95] S. Valsalam, P. Agastian, M.V. Arasu, N.A. Al-Dhabi, A.K.M. Ghilan, K. Kaviyarasu, B. Ravindran, S.W. Chang, S. Arokiyaraj, Rapid biosynthesis and characterization of silver nanoparticles from the leaf extract of Tropaeolum majus L. and its enhanced *in-vitro* antibacterial, antifungal, antioxidant and anticancer properties, J. Photochem. Photobiol. B Biol. 191 (2019) 65–74.
[96] L. He, H. Wu, S. Gao, X. Liao, Q. He, B. Shi, Silver nanoparticles stabilized by tannin grafted collagen fiber: synthesis, characterization and antifungal activity, Ann. Microbiol. 62 (1) (2012) 319–327.
[97] Z.K. Xia, Q.H. Ma, S.Y. Li, D.Q. Zhang, L. Cong, Y.L. Tian, R.Y. Yang, The antifungal effect of silver nanoparticles on Trichosporon asahii, J. Microbiol. Immunol. Infect. 49 (2) (2016) 182–188.
[98] P. Soleimani, A. Mehrvar, J. Michaud, N. Vaez, Optimization of silver nanoparticle biosynthesis by entomopathogenic fungi and assays of their antimicrobial and antifungal properties, J. Invertebr. Pathol. 190 (2022) 107749.
[99] S. Tang, J. Zheng, Antibacterial activity of silver nanoparticles: structural effects, Adv. Healthc. Mater. 7 (13) (2018) 1701503.
[100] A. Gibała, P. Żeliszewska, T. Gosiewski, A. Krawczyk, D. Duraczyńska, J. Szaleniec, M. Szaleniec, M. Oćwieja, Antibacterial and antifungal properties of silver nanoparticles-effect of a surface-stabilizing agent, Biomolecules 11 (10) (2021) 1481.
[101] A. Nabikhan, K. Kandasamy, A. Raj, N.M. Alikunhi, Synthesis of antimicrobial silver nanoparticles by callus and leaf extracts from saltmarsh plant, Sesuvium portulacastrum L, Colloids Surf. B. Biointerfaces 79 (2) (2010) 488–493.
[102] O. Choi, C.P. Yu, G.E. Fernández, Z. Hu, Interactions of nanosilver with Escherichia coli cells in planktonic and biofilm cultures, Water Res. 44 (20) (2010) 6095–6103.
[103] X. Liu, J. Chen, C. Qu, G. Bo, L. Jiang, H. Zhao, J. Zhang, Y. Lin, Y. Hua, P. Yang, A mussel-inspired facile method to prepare multilayer-AgNP-loaded contact lens for early treatment of bacterial and fungal keratitis, ACS Biomater. Sci. Eng. 4 (5) (2018) 1568–1579.
[104] E.J.J. Mallmann, F.A. Cunha, B.N. Castro, A.M. Maciel, E.A. Menezes, P.B.A. Fechine, Antifungal activity of silver nanoparticles obtained by green synthesis, Rev. Inst. Med. Trop. São Paulo 57 (2) (2015) 165–167.
[105] A. Nasrollahi, K. Pourshamsian, P. Mansourkiaee, Antifungal activity of silver nanoparticles on some of fungi, Int. J. Nano Dimens. 1 (3) (2011) 233.
[106] C.G. Kumar, Y. Poornachandra, Biodirected synthesis of Miconazole-conjugated bacterial silver nanoparticles and their application as antifungal agents and drug delivery vehicles, Colloids Surf. B Biointerfaces 125 (2015) 110–119.
[107] E. Silva, S.M. Saraiva, S.P. Miguel, I.J. Correia, PVP-coated silver nanoparticles showing antifungal improved activity against dermatophytes, J. Nanopart. Res. 16 (11) (2014) 2726.
[108] J.J.A. Bonilla, D.J.P. Guerrero, C.I.S. Suárez, C.C.O. López, R.G.T. Sáez, *In vitro* antifungal activity of silver nanoparticles against fluconazole-resistant Candida species, World J. Microbiol. Biotechnol. 31 (11) (2015) 1801–1809.
[109] A. Bankar, B. Joshi, A.R. Kumar, S. Zinjarde, Banana peel extract mediated synthesis of gold nanoparticles, Colloids Surf. B Biointerfaces 80 (1) (2010) 45–50.
[110] S. Smitha, K. Gopchandran, Surface enhanced Raman scattering, antibacterial and antifungal active triangular gold nanoparticles, Spectrochim. Acta Part A 102 (2013) 114–119.
[111] J.V. Gopal, M. Thenmozhi, K. Kannabiran, G. Rajakumar, K. Velayutham, A.A. Rahuman, Actinobacteria mediated synthesis of gold nanoparticles using Streptomyces sp. VITDDK3 and its antifungal activity, Mater. Lett. 93 (2013) 360–362.
[112] M. Eskandari-Nojedehi, H. Jafarizadeh-Malmiri, J. Rahbar-Shahrouzi, Hydrothermal green synthesis of gold nanoparticles using mushroom (Agaricus bisporus) extract: physico-chemical characteristics and antifungal activity studies, Green Process. Synth. 7 (1) (2018) 38–47.
[113] I.A. Wani, T. Ahmad, Size and shape dependant antifungal activity of gold nanoparticles: a case study of Candida, Colloids Surf. B Biointerfaces 101 (2013) 162–170.
[114] T. Ahmad, I.A. Wani, I.H. Lone, A. Ganguly, N. Manzoor, A. Ahmad, J. Ahmed, A.S. Al-Shihri, Antifungal activity of gold nanoparticles prepared by solvothermal method, Mater. Res. Bull. 48 (1) (2013) 12–20.
[115] S. Swain, S. Barik, T. Behera, S. Nayak, S. Sahoo, S. Mishra, P. Swain, Green synthesis of gold nanoparticles using root and leaf extracts of Vetiveria zizanioides and Cannabis sativa and its antifungal activities, BioNanoScience 6 (3) (2016) 205–213.
[116] S. Dananjaya, N.T. Thao, H. Wijerathna, J. Lee, M. Edussuriya, D. Choi, R.S. Kumar, *In vitro* and *in vivo* anticandidal efficacy of green synthesized gold nanoparticles using Spirulina maxima polysaccharide, Process Biochem. 92 (2020) 138–148.
[117] J. Ramyadevi, K. Jeyasubramanian, A. Marikani, G. Rajakumar, A.A. Rahuman, Synthesis and antimicrobial activity of copper nanoparticles, Mater. Lett. 71 (2012) 114–116.
[118] M.S. Usman, M.E. El Zowalaty, K. Shameli, N. Zainuddin, M. Salama, N.A. Ibrahim, Synthesis, characterization, and antimicrobial properties of copper nanoparticles, Int. J. Nanomed. 8 (2013) 4467.
[119] P.V. Viet, H.T. Nguyen, T.M. Cao, L.V. Hieu, Fusarium antifungal activities of copper nanoparticles synthesized by a chemical reduction method, J. Nanomater. 2016 (2016) 6.
[120] K. Bramhanwade, S. Shende, S. Bonde, A. Gade, M. Rai, Fungicidal activity of Cu nanoparticles against Fusarium causing crop diseases, Environ. Chem. Lett. 14 (2) (2016) 229–235.
[121] P. Kanhed, S. Birla, S. Gaikwad, A. Gade, A.B. Seabra, O. Rubilar, N. Duran, M. Rai, *In vitro* antifungal efficacy of copper nanoparticles against selected crop pathogenic fungi, Mater. Lett. 115 (2014) 13–17.

[122] S. Tantubay, S.K. Mukhopadhyay, H. Kalita, S. Konar, S. Dey, A. Pathak, P. Pramanik, Carboxymethylated chitosan-stabilized copper nanoparticles: a promise to contribute a potent antifungal and antibacterial agent, J. Nanopart. Res. 17 (6) (2015) 243.
[123] V.D. Cao, P.P. Nguyen, V.Q. Khuong, C.K. Nguyen, X.C. Nguyen, C.H. Dang, N.Q. Tran, Ultrafine copper nanoparticles exhibiting a powerful antifungal/killing activity against Corticium salmonicolor, Bull. Korean Chem. Soc. 35 (9) (2014) 2645–2648.
[124] N. Cioffi, L. Torsi, N. Ditaranto, G. Tantillo, L. Ghibelli, L. Sabbatini, T. Bleve-Zacheo, M. D'Alessio, P.G. Zambonin, E. Traversa, Copper nanoparticle/polymer composites with antifungal and bacteriostatic properties, Chem. Mater. 17 (21) (2005) 5255–5262.
[125] N. Cioffi, L. Torsi, N. Ditaranto, L. Sabbatini, P.G. Zambonin, G. Tantillo, L. Ghibelli, M. D'Alessio, T. Bleve-Zacheo, E. Traversa, Antifungal activity of polymer-based copper nanocomposite coatings, Appl. Phys. Lett. 85 (12) (2004) 2417–2419.
[126] D. South, in: Inorganic Pesticides, Encyclopedia of pest management, Marcel Dekker, Inc., New York, 2002, pp. 395–397.
[127] A. Wani, M. Shah, A unique and profound effect of MgO and ZnO nanoparticles on some plant pathogenic fungi, J. Appl. Pharm. Sci. 2 (3) (2012) 4.
[128] T. Surendra, S.M. Roopan, N.A. Al-Dhabi, M.V. Arasu, G. Sarkar, K. Suthindhiran, Vegetable peel waste for the production of ZnO nanoparticles and its toxicological efficiency, antifungal, hemolytic, and antibacterial activities, Nanoscale Res. Lett. 11 (1) (2016) 546.
[129] S. Vlad, C. Tanase, D. Macocinschi, C. Ciobanu, T. Balaes, D. Filip, I. Gostin, L. Gradinaru, Antifungal behaviour of polyurethane membranes with zinc oxide nanoparticles, Dig. J. Nanomater. Biostruct. 7 (2012) 51–58.
[130] S. Gunalan, R. Sivaraj, V. Rajendran, Green synthesized ZnO nanoparticles against bacterial and fungal pathogens, Prog. Nat. Sci. Mater. Int. 22 (6) (2012) 693–700.
[131] S. Senthilkumar, T. Sivakumar, Green tea (Camellia sinensis) mediated synthesis of zinc oxide (ZnO) nanoparticles and studies on their antimicrobial activities, Int. J. Pharm. Pharm. Sci. 6 (6) (2014) 461–465.
[132] L. He, Y. Liu, A. Mustapha, M. Lin, Antifungal activity of zinc oxide nanoparticles against Botrytis cinerea and Penicillium expansum, Microbiol. Res. 166 (3) (2011) 207–215.
[133] A.M. Pillai, V.S. Sivasankarapillai, A. Rahdar, J. Joseph, F. Sadeghfar, K. Rajesh, G.Z. Kyzas, Green synthesis and characterization of zinc oxide nanoparticles with antibacterial and antifungal activity, J. Mol. Struct. 1211 (2020) 128107.
[134] P. Arciniegas-Grijalba, M. Patiño-Portela, L. Mosquera-Sánchez, J. Guerrero–Vargas, J. Rodríguez-Páez, ZnO nanoparticles (ZnO-NPs) and their antifungal activity against coffee fungus Erythricium salmonicolor, Appl. Nanosci. 7 (5) (2017) 225–241.
[135] C.O. Dimkpa, D.E. Latta, J.E. McLean, D.W. Britt, M.I. Boyanov, A.J. Anderson, Fate of CuO and ZnO nano-and microparticles in the plant environment, Environ. Sci. Technol. 47 (9) (2013) 4734–4742.
[136] E.M. El-Diasty, M. Ahmed, N. Okasha, S.F. Mansour, S.I. El-Dek, H. El-Khalek, M.H. Youssif, Antifungal activity of zinc oxide nanoparticles against dermatophytic lesions of cattle, Rom. J. Biophys. 23 (2013) 191–202.
[137] N. Tiwari, R. Pandit, S. Gaikwad, A. Gade, M. Rai, Biosynthesis of zinc oxide nanoparticles by petals extract of Rosa indica L., its formulation as nail paint and evaluation of antifungal activity against fungi causing onychomycosis, IET Nanobiotechnol. 11 (2) (2016) 205–211.
[138] D. Sharma, J. Rajput, B. Kaith, M. Kaur, S. Sharma, Synthesis of ZnO nanoparticles and study of their antibacterial and antifungal properties, Thin Solid Films 519 (3) (2010) 1224–1229.
[139] D. Sharma, S. Sharma, B.S. Kaith, J. Rajput, M. Kaur, Synthesis of ZnO nanoparticles using surfactant free in-air and microwave method, Appl. Surf. Sci. 257 (22) (2011) 9661–9672.
[140] A. Lipovsky, Y. Nitzan, A. Gedanken, R. Lubart, Antifungal activity of ZnO nanoparticles-the role of ROS mediated cell injury, Nanotechnology 22 (10) (2011) 105101.
[141] P. Singh, A. Nanda, Antimicrobial and antifungal potential of zinc oxide nanoparticles in comparison to conventional zinc oxide particles, J. Chem. Pharm. Res. 5 (11) (2013) 457–463.
[142] A. Lipovsky, Z. Tzitrinovich, H. Friedmann, G. Applerot, A. Gedanken, R. Lubart, EPR study of visible light-induced ROS generation by nanoparticles of ZnO, J. Phys. Chem. C 113 (36) (2009) 15997–16001.
[143] K. Kairyte, A. Kadys, Z. Luksiene, Antibacterial and antifungal activity of photoactivated ZnO nanoparticles in suspension, J. Photochem. Photobiol. B Biol. 128 (2013) 78–84.
[144] P. Jamdagni, P. Khatri, J. Rana, Green synthesis of zinc oxide nanoparticles using flower extract of Nyctanthes arbor-tristis and their antifungal activity, J. King Saud Univ. Sci. 30 (2) (2018) 168–175.
[145] P. Jamdagni, J.S. Rana, P. Khatri, K. Nehra, Comparative account of antifungal activity of green and chemically synthesized zinc oxide nanoparticles in combination with agricultural fungicides, Int. J. Nano Dimens. 9 (2) (2018) 198–208.
[146] N.N. Ilkhechi, M. Mozammel, A.Y. Khosroushahi, Antifungal effects of ZnO, TiO_2 and ZnO-TiO_2 nanostructures on Aspergillus flavus, Pestic. Biochem. Physiol. 176 (2021) 104869.
[147] L. Palanikumar, S.N. Ramasamy, C. Balachandran, Size-dependent antimicrobial response of zinc oxide nanoparticles, IET Nanobiotechnol. 8 (2) (2014) 111–117.
[148] A. Karimiyan, H. Najafzadeh, M. Ghorbanpour, S.H. Hekmati-Moghaddam, Antifungal effect of magnesium oxide, zinc oxide, silicon oxide and copper oxide nanoparticles against Candida albicans, Zahedan J. Res. Med. Sci. 17 (10) (2015) e2179.
[149] A. Miri, M. Khatami, O. Ebrahimy, M. Sarani, Cytotoxic and antifungal studies of biosynthesized zinc oxide nanoparticles using extract of Prosopis farcta fruit, Green Chem. Lett. Rev. 13 (1) (2020) 27–33.
[150] A.S.H. Hameed, C. Karthikeyan, V.S. Kumar, S. Kumaresan, S. Sasikumar, Effect of Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} metal ions on the antifungal activity of ZnO nanoparticles tested against Candida albicans, Mater. Sci. Eng. C 52 (2015) 171–177.
[151] C. Contado, A. Pagnoni, TiO_2 in commercial sunscreen lotion: flow field-flow fractionation and ICP-AES together for size analysis, Anal. Chem. 80 (19) (2008) 7594–7608.
[152] F. Haghighi, S. Roudbar Mohammadi, P. Mohammadi, S. Hosseinkhani, R. Shipour, Antifungal activity of TiO2 nanoparticles and EDTA on Candida albicans biofilms, Infect. Epidemiol. Microbiol. 1 (1) (2013) 33–38.
[153] S. Darbari, Y. Abdi, F. Haghighi, S. Mohajerzadeh, N. Haghighi, Investigating the antifungal activity of TiO_2 nanoparticles deposited on branched carbon nanotube arrays, J. Phys. D Appl. Phys. 44 (24) (2011) 245401.
[154] H. Hitkova, A. Stoyanova, N. Ivanova, M. Sredkova, V. Popova, R. Iordanova, A. Bachvarova-Nedelcheva, Study of antibacterial activity of nonhydrolytic synthesized TiO2 against E. coli, P. aeruginosa and S. aureus, J. Optoelectron. Biomed. Mater. 4 (1) (2012) 9–17.
[155] R. Prucek, J. Tuček, M. Kilianová, A. Panáček, L. Kvítek, J. Filip, M. Kolář, K. Tománková, R. Zbořil, The targeted antibacterial and antifungal properties of magnetic nanocomposite of iron oxide and silver nanoparticles, Biomaterials 32 (21) (2011) 4704–4713.
[156] J.S. Weinstein, C.G. Varallyay, E. Dosa, S. Gahramanov, B. Hamilton, W.D. Rooney, L.L. Muldoon, E.A. Neuwelt, Superparamagnetic iron oxide nanoparticles: diagnostic magnetic resonance imaging and potential therapeutic applications in neurooncology and central nervous system inflammatory pathologies, a review, J. Cereb. Blood Flow Metab. 30 (1) (2010) 15–35.
[157] S.A. Wahajuddin, Superparamagnetic iron oxide nanoparticles: magnetic nanoplatforms as drug carriers, Int. J. Nanomed. 7 (2012) 3445.
[158] F.M. Kievit, M. Zhang, Surface engineering of iron oxide nanoparticles for targeted cancer therapy, Acc. Chem. Res. 44 (10) (2011) 853–862.
[159] J. Jafari, X.L. Han, J. Palmer, P.A. Tran, A.J. O'Connor, Remote control in formation of 3D multicellular assemblies using magnetic forces, ACS Biomater. Sci. Eng. 5 (5) (2019) 2532–2542.
[160] S. Parveen, A.H. Wani, M.A. Shah, H.S. Devi, M.Y. Bhat, J.A. Koka, Preparation, characterization and antifungal activity of iron oxide nanoparticles, Microb. Pathog. 115 (2018) 287–292.
[161] N.S. Seddighi, S. Salari, A.R. Izadi, Evaluation of antifungal effect of iron-oxide nanoparticles against different Candida species, IET Nanobiotechnol. 11 (7) (2017) 883–888.
[162] F. Golipour, R. Habibipour, L. Moradihaghgou, Investigating effects of superparamagnetic iron oxide nanoparticles on Candida albicans biofilm formation, Med. Lab. J. 13 (6) (2019) 44–50.
[163] A. Wilczewska, A. Kosińska, I. Misztalewska-Turkowicz, A. Kubicka, K. Niemirowicz-Laskowska, K. Markiewicz, R. Bucki, G. Celichowski, B. Kalska-Szostko, B. Rudolf, Magnetic nanoparticles bearing metallocarbonyl moiety as antibacterial and antifungal agents, Appl. Surf. Sci. 487 (2019) 601–609.
[164] P. Basu, J. Chakraborty, N. Ganguli, K. Mukherjee, K. Acharya, B. Satpati, S. Khamrui, S. Mandal, D. Banerjee, D. Goswami, Defect-engineered MoS2 nanostructures for reactive oxygen species generation in the dark: antipollutant and antifungal performances, ACS Appl. Mater. Interfaces 11 (51) (2019) 48179–48191.
[165] S. Saha, M.S. Gilliam, Q.H. Wang, A.A. Green, Eradication of fungi using $MoSe_2$/chitosan nanosheets, ACS Appl. Nano Mater. 5 (1) (2022) 133–148.
[166] T. Huang, J.A. Holden, D.E. Heath, N.M. O'Brien-Simpson, A.J. O'Connor, Engineering highly effective antimicrobial selenium nanoparticles through control of particle size, Nanoscale 11 (2019) 14937–14951.
[167] T. Huang, S. Kumari, H. Herold, H. Bargel, T.B. Aigner, D.E. Heath, N.M. O'Brien-Simpson, A.J. O'Connor, T. Scheibel, Enhanced antibacterial activity of Se nanoparticles upon coating with recombinant spider silk protein eADF4(κ16), Int. J. Nanomed. 2020 (15) (2020) 4275–4288.
[168] H.H. Lara, G. Guisbiers, J. Mendoza, L.C. Mimun, B.A. Vincent, J.L. Lopez-Ribot, K.L. Nash, Synergistic antifungal effect of chitosan-stabilized selenium nanoparticles synthesized by pulsed laser ablation in liquids against Candida albicans biofilms, Int. J. Nanomed. 13 (2018) 2697.
[169] J. Yip, L. Liu, K.H. Wong, P.H. Leung, C.W.M. Yuen, M.C. Cheung, Investigation of antifungal and antibacterial effects of fabric padded with highly stable selenium nanoparticles, J. Appl. Polym. Sci. 131 (17) (2014) 40728.
[170] F.M. Mosallam, G.S. El-Sayyad, R.M. Fathy, A.I. El-Batal, Biomolecules-mediated synthesis of selenium nanoparticles using Aspergillus oryzae fermented Lupin extract and gamma radiation for hindering the growth of some multidrug-resistant bacteria and pathogenic fungi, Microb. Pathog. 122 (2018) 108–116.
[171] M.H. Bafghi, M. Darroudi, M. Zargar, H. Zarrinfar, R. Nazari, Biosynthesis of selenium nanoparticles by Aspergillus flavus and Candida albicans for antifungal applications, Micro Nano Lett. 16 (14) (2021) 656–669.
[172] M. Shakibaie, N.S. Mohazab, S.A.A. Mousavi, Antifungal activity of selenium nanoparticles synthesized by Bacillus species Msh-1 against Aspergillus fumigatus and Candida albicans, Jundishapur J. Microbiol. 8 (9) (2015) e26381.
[173] E. Cremonini, E. Zonaro, M. Donini, S. Lampis, M. Boaretti, S. Dusi, P. Melotti, M.M. Lleo, G. Vallini, Biogenic selenium nanoparticles: characterization, an-

timicrobial activity and effects on human dendritic cells and fibroblasts, Microb. Biotechnol. 9 (6) (2016) 758–771.
[174] M.H. Bafghi, R. Nazari, M. Darroudi, M. Zargar, H. Zarrinfar, The effect of biosynthesized selenium nanoparticles on the expression of CYP51A and HSP90 antifungal resistance genes in Aspergillus fumigatus and Aspergillus flavus, Biotechnol. Prog. 38 (1) (2022) e3206.
[175] Z. Peng, X. Liu, W. Zhang, Z. Zeng, Z. Liu, C. Zhang, Y. Liu, B. Shao, Q. Liang, W. Tang, Advances in the application, toxicity and degradation of carbon nanomaterials in environment: a review, Environ. Int. 134 (2020) 105298.
[176] X. Wang, C. Liu, H. Li, H. Zhang, R. Ma, Q. Zhang, F. Yang, Y.C. Liao, W. Yuan, F. Chen, Metabonomics-assisted label-free quantitative proteomic and transcriptomic analysis reveals novel insights into the antifungal effect of graphene oxide for controlling Fusarium graminearum, Environ. Sci. Nano 6 (11) (2019) 3401–3421.
[177] X. Wang, X. Liu, J. Chen, H. Han, Z. Yuan, Evaluation and mechanism of antifungal effects of carbon nanomaterials in controlling plant fungal pathogen, Carbon 68 (2014) 798–806.
[178] Y. Hao, X. Cao, C. Ma, Z. Zhang, N. Zhao, A. Ali, T. Hou, Z. Xiang, J. Zhuang, S. Wu, Potential applications and antifungal activities of engineered nanomaterials against gray mold disease agent Botrytis cinerea on rose petals, Front. Plant Sci. 8 (2017) 1332.
[179] N. Meena, Y. Sahni, D. Thakur, R. Singh, Applications of nanotechnology in veterinary therapeutics, J. Entomol. Zool. Stud. 6 (2) (2018) 167–175.
[180] J.T. Cang-Rong, G. Pastorin, The influence of carbon nanotubes on enzyme activity and structure: investigation of different immobilization procedures through enzyme kinetics and circular dichroism studies, Nanotechnology 20 (25) (2009) 255102.
[181] A. Jurj, C. Braicu, L.A. Pop, C. Tomuleasa, C.D. Gherman, I. Berindan-Neagoe, The new era of nanotechnology, an alternative to change cancer treatment, Drug Des. Dev. Ther. 11 (2017) 2871.
[182] X. Yuan, X. Zhang, L. Sun, Y. Wei, X. Wei, Cellular toxicity and immunological effects of carbon-based nanomaterials, Part. Fibre Toxicol. 16 (1) (2019) 1–27.
[183] P. Velmurugan, J. Shim, K. Kim, B.T. Oh, Prunus× yedoensis tree gum mediated synthesis of platinum nanoparticles with antifungal activity against phytopathogens, Mater. Lett. 174 (2016) 61–65.
[184] F.J. Osonga, S. Kalra, R.M. Miller, D. Isika, O.A. Sadik, Synthesis, characterization and antifungal activities of eco-friendly palladium nanoparticles, RSC Adv. 10 (10) (2020) 5894–5904.
[185] M.R. Kamli, V. Srivastava, N.H. Hajrah, J.S. Sabir, A. Ali, M.A. Malik, A. Ahmad, Phytogenic fabrication of Ag–Fe bimetallic nanoparticles for cell cycle arrest and apoptosis signaling pathways in candida auris by generating oxidative stress, Antioxidants 10 (2) (2021) 182.
[186] M.R. Kamli, E.A. Alzahrani, S.M. Albukhari, A. Ahmad, J.S. Sabir, M.A. Malik, Combination effect of novel bimetallic Ag-Ni nanoparticles with fluconazole against Candida albicans, J. Fungi 8 (7) (2022) 733.
[187] M.R. Kamli, M.A. Malik, S.A. Lone, J.S. Sabir, E.H. Mattar, A. Ahmad, Beta vulgaris assisted fabrication of novel Ag-Cu bimetallic nanoparticles for growth inhibition and virulence in Candida albicans, Pharmaceutics 13 (11) (2021) 1957.
[188] M.R. Kamli, V. Srivastava, N.H. Hajrah, J.S. Sabir, K.R. Hakeem, A. Ahmad, M.A. Malik, Facile bio-fabrication of Ag-Cu-Co trimetallic nanoparticles and its fungicidal activity against Candida auris, J. Fungi 7 (1) (2021) 62.
[189] ASTM International, Standard practice for assessment of hemolytic properties of materials, F756–08 (2008).
[190] R. Sivaraj, P.K. Rahman, P. Rajiv, S. Narendhran, R. Venckatesh, Biosynthesis and characterization of Acalypha indica mediated copper oxide nanoparticles and evaluation of its antimicrobial and anticancer activity, Spectrochim. Acta Part A 129 (2014) 255–258.
[191] A. Muñoz-Escobar, S.Y. Reyes-López, Antifungal susceptibility of Candida species to copper oxide nanoparticles on polycaprolactone fibers (PCL-CuONPs), PLoS One 15 (2) (2020) e0228864.
[192] P. Vanathi, P. Rajiv, R. Sivaraj, Synthesis and characterization of Eichhornia–mediated copper oxide nanoparticles and assessing their antifungal activity against plant pathogens, Bull. Mater. Sci. 39 (5) (2016) 1165–1170.
[193] D. Devipriya, S.M. Roopan, Cissus quadrangularis mediated ecofriendly synthesis of copper oxide nanoparticles and its antifungal studies against Aspergillus niger, Aspergillus flavus, Mater. Sci. Eng. C 80 (2017) 38–44.
[194] M. Shenashen, A. Derbalah, A. Hamza, A. Mohamed, S. El Safty, Antifungal activity of fabricated mesoporous alumina nanoparticles against root rot disease of tomato caused by Fusarium oxysporium, Pest Manag. Sci. 73 (6) (2017) 1121–1126.
[195] M.A. Parizi, Y. Moradpour, A. Roostaei, M. Khani, M. Negahdari, G. Rahimi, Evaluation of the antifungal effect of magnesium oxide nanoparticles on Fusarium oxysporum F. Sp. lycopersici, pathogenic agent of tomato, Eur. J. Exp. Biol. 4 (3) (2014) 151–156.
[196] S. Gowri, R.R. Gandhi, M. Sundrarajan, Structural, optical, antibacterial and antifungal properties of zirconia nanoparticles by biobased protocol, J. Mater. Sci. Technol. 30 (8) (2014) 782–790.
[197] R. Hernandez-Delgadillo, D. Velasco-Arias, J.J. Martinez-Sanmiguel, D. Diaz, I. Zumeta-Dube, K. Arevalo-Niño, C. Cabral-Romero, Bismuth oxide aqueous colloidal nanoparticles inhibit Candida albicans growth and biofilm formation, Int. J. Nanomed. 8 (2013) 1645.
[198] S.R. Choudhury, M. Ghosh, A. Mandal, D. Chakravorty, M. Pal, S. Pradhan, A. Goswami, Surface-modified sulfur nanoparticles: an effective antifungal agent against Aspergillus niger and Fusarium oxysporum, Appl. Microbiol. Biotechnol. 90 (2) (2011) 733–743.
[199] G.M. Soliman, Nanoparticles as safe and effective delivery systems of antifungal agents: achievements and challenges, Int. J. Pharm. 523 (1) (2017) 15–32.
[200] C.S. Paulo, M. Vidal, L.S. Ferreira, Antifungal nanoparticles and surfaces, Biomacromolecules 11 (10) (2010) 2810–2817.
[201] M.M. Lino, C.S. Paulo, A.C. Vale, M.F. Vaz, L.S. Ferreira, Antifungal activity of dental resins containing amphotericin B-conjugated nanoparticles, Dent. Mater. 29 (10) (2013) e252–e262.
[202] D. Botequim, J. Maia, M. Lino, L. Lopes, P. Simoes, L. Ilharco, L. Ferreira, Nanoparticles and surfaces presenting antifungal, antibacterial and antiviral properties, Langmuir 28 (20) (2012) 7646–7656.
[203] K. Tutaj, R. Szlazak, K. Szalapata, J. Starzyk, R. Luchowski, W. Grudzinski, M. Osinska-Jaroszuk, A. Jarosz-Wilkolazka, A. Szuster-Ciesielska, W.I. Gruszecki, Amphotericin B-silver hybrid nanoparticles: synthesis, properties and antifungal activity, Nanomed. Nanotechnol. Biol. Med. 12 (4) (2016) 1095–1103.
[204] S.D. Oh, S. Lee, S.H. Choi, I.S. Lee, Y.M. Lee, J.H. Chun, H.J. Park, Synthesis of Ag and Ag–SiO_2 nanoparticles by γ-irradiation and their antibacterial and antifungal efficiency against Salmonella enterica serovar Typhimurium and Botrytis cinerea, Colloids Surf. Physicochem. Eng. Asp. 275 (1-3) (2006) 228–233.
[205] Y. Liu, H. Ren, D. Wang, M. Zhang, S. Sun, Y. Zhao, The synergistic antifungal effects of gypenosides combined with fluconazole against resistant Candida albicans via inhibiting the drug efflux and biofilm formation, Biomed. Pharmacother. 130 (2020) 110580.
[206] M. Singh, M. Kumar, R. Kalaivani, S. Manikandan, A. Kumaraguru, Metallic silver nanoparticle: a therapeutic agent in combination with antifungal drug against human fungal pathogen, Bioprocess Biosyst. Eng. 36 (4) (2013) 407–415.
[207] M. Gajbhiye, J. Kesharwani, A. Ingle, A. Gade, M. Rai, Fungus-mediated synthesis of silver nanoparticles and their activity against pathogenic fungi in combination with fluconazole, Nanomed. Nanotechnol. Biol. Med. 5 (4) (2009) 382–386.
[208] F. Noorbakhsh, S. Rezaie, A.R. Shahverdi, Antifungal effects of silver nanoparticle alone and with combination of antifungal drug on dermatophyte pathogen Trichophyton rubrum, in: Proceedings of the International Conference on Bioscience, Biochemistry and Bioinformatics, 2011, pp. 364–367.
[209] C. Longhi, J.P. Santos, A.T. Morey, P.D. Marcato, N. Durán, P. Pinge-Filho, G. Nakazato, S.F. Yamada-Ogatta, L.M. Yamauchi, Combination of fluconazole with silver nanoparticles produced by Fusarium oxysporum improves antifungal effect against planktonic cells and biofilm of drug-resistant Candida albicans, Sabouraudia 54 (4) (2015) 428–432.
[210] D.R. Monteiro, S. Silva, M. Negri, L.F. Gorup, E.R. de Camargo, R. Oliveira, D.B. Barbosa, M. Henriques, Antifungal activity of silver nanoparticles in combination with nystatin and chlorhexidine digluconate against C andida albicans and C andida glabrata biofilms, Mycoses 56 (6) (2013) 672–680.
[211] S. Rajeshkumar, C. Malarkodi, M. Vanaja, G. Annadurai, Anticancer and enhanced antimicrobial activity of biosynthesizd silver nanoparticles against clinical pathogens, J. Mol. Struct. 1116 (2016) 165–173.
[212] P. Jamdagni, J. Rana, P. Khatri, Antioxidant activity and antifungal fractional inhibitory concentration indices of zinc oxide nanoparticles in combination with carbendazim, mancozeb, and thiram, Micro Nano Lett. 14 (10) (2019) 1037–1040.
[213] I.S. Weitz, M. Maoz, D. Panitz, S. Eichler, E. Segal, Combination of CuO nanoparticles and fluconazole: preparation, characterization, and antifungal activity against Candida albicans, J. Nanopart. Res. 17 (8) (2015) 342.
[214] M. Sardar, W. Ahmed, S. Al Ayoubi, S. Nisa, Y. Bibi, M. Sabir, M.M. Khan, W. Ahmed, A. Qayyum, Fungicidal synergistic effect of biogenically synthesized zinc oxide and copper oxide nanoparticles against Alternaria citri causing citrus black rot disease, Saudi J. Biol. Sci. 29 (1) (2022) 88–95.
[215] S. Mansoor, I. Zahoor, T.R. Baba, S.A. Padder, Z. Bhat, A.M. Koul, L. Jiang, Fabrication of silver nanoparticles against fungal pathogens, Front. Nanotechnol. 3 (2021) 679358.
[216] I.s. Hwang, J. Lee, J.H. Hwang, K.J. Kim, D.G. Lee, Silver nanoparticles induce apoptotic cell death in Candida albicans through the increase of hydroxyl radicals, FEBS J. 279 (7) (2012) 1327–1338.
[217] D. Jia, W. Sun, Silver nanoparticles offer a synergistic effect with fluconazole against fluconazole-resistant Candida albicans by abrogating drug efflux pumps and increasing endogenous ROS, Infection, Genet. Evol. 93 (2021) 104937.
[218] L.P. Zheng, Z. Zhang, B. Zhang, J.W. Wang, Antifungal properties of Ag-SiO_2 core-shell nanoparticles against phytopathogenic fungi, Adv. Mater. Res. (2012) 814–818 Trans Tech Publ.
[219] I. Sondi, B. Salopek-Sondi, Silver nanoparticles as antimicrobial agent: a case study on E. coli as a model for Gram-negative bacteria, J. Colloid Interface Sci. 275 (1) (2004) 177–182.
[220] A. Panáček, L. Kvitek, R. Prucek, M. Kolář, R. Večeřová, N. Pizúrová, V.K. Sharma, T.J. Nevěčná, R. Zbořil, Silver colloid nanoparticles: synthesis, characterization, and their antibacterial activity, J. Phys. Chem. B 110 (33) (2006) 16248–16253.
[221] M. Rai, A. Yadav, A. Gade, Silver nanoparticles as a new generation of antimicrobials, Biotechnol. Adv. 27 (2009) 76–83.
[222] S.W. Kim, K.S. Kim, K. Lamsal, Y.J. Kim, S.B. Kim, M. Jung, S.J. Sim, H.S. Kim, S.J. Chang, J.K. Kim, An *in vitro* study of the antifungal effect of silver nanoparticles on oak wilt pathogen Raffaelea sp, J. Microbiol. Biotechnol. 19 (8) (2009) 760–764.
[223] M. Selvaraj, P. Pandurangan, N. Ramasami, S.B. Rajendran, S.N. Sangilimuthu, P. Perumal, Highly potential antifungal activity of quantum-sized silver

nanoparticles against Candida albicans, Appl. Biochem. Biotechnol. 173 (1) (2014) 55–66.
[224] P. Prasher, M. Singh, H. Mudila, Green synthesis of silver nanoparticles and their antifungal properties, BioNanoScience 8 (1) (2018) 254–263.
[225] C. Li, X. Wang, F. Chen, C. Zhang, X. Zhi, K. Wang, D. Cui, The antifungal activity of graphene oxide–silver nanocomposites, Biomaterials 34 (15) (2013) 3882–3890.
[226] R. Vazquez-Muñoz, M. Avalos-Borja, E. Castro-Longoria, Ultrastructural analysis of Candida albicans when exposed to silver nanoparticles, PLoS One 9 (10) (2014) e108876.
[227] S.M. Ouda, Antifungal activity of silver and copper nanoparticles on two plant pathogens, Alternaria alternata and Botrytis cinerea, Res. J. Microbiol. 9 (1) (2014) 34–42.
[228] K. Lamsa, S.W. Kim, J.H. Jung, Y.S. Kim, K.S. Kim, Y.S. Lee, Inhibition effects of silver nanoparticles against powdery mildews on cucumber and pumpkin, Mycobiology 39 (1) (2011) 26–32.
[229] K.B. Narayanan, H.H. Park, Antifungal activity of silver nanoparticles synthesized using turnip leaf extract (Brassica rapa L.) against wood rotting pathogens, Eur. J. Plant Pathol. 140 (2) (2014) 185–192.
[230] V. Gopinath, P. Velusamy, Extracellular biosynthesis of silver nanoparticles using Bacillus sp. GP-23 and evaluation of their antifungal activity towards Fusarium oxysporum, Spectrochim. Acta Part A 106 (2013) 170–174.
[231] K. Lamsal, S.W. Kim, J.H. Jung, Y.S. Kim, K.S. Kim, Y.S. Lee, Application of silver nanoparticles for the control of Colletotrichum species *in vitro* and pepper anthracnose disease in field, Mycobiology 39 (3) (2011) 194–199.
[232] M. Zawrah, S.A. El-Moez, D. Center, Antimicrobial activities of gold nanoparticles against major foodborne pathogens, Life Sci. J. 8 (4) (2011) 37–44.
[233] K.G. Akpomie, S. Ghosh, M. Gryzenhout, J. Conradie, One-pot synthesis of zinc oxide nanoparticles via chemical precipitation for bromophenol blue adsorption and the antifungal activity against filamentous fungi, Sci. Rep. 11 (1) (2021) 1–17.
[234] J. Xue, Z. Luo, P. Li, Y. Ding, Y. Cui, Q. Wu, A residue-free green synergistic antifungal nanotechnology for pesticide thiram by ZnO nanoparticles, Sci. Rep. 4 (2014) 5408.
[235] M. AbdElhady, Preparation and characterization of chitosan/zinc oxide nanoparticles for imparting antimicrobial and UV protection to cotton fabric, Int. J. Carbohydr. Chem. 2012 (2012).
[236] S. Abdeen, R.R. Isaac, S. Geo, S. Sornalekshmi, A. Rose, P. Praseetha, Evaluation of antimicrobial activity of biosynthesized iron and silver nanoparticles using the fungi fusarium oxysporum and actinomycetes sp. on human pathogens, Nano Biomed. Eng. 5 (1) (2013) 39–45.
[237] M.J. Kasprowicz, M. Kozioł, A. Gorczyca, The effect of silver nanoparticles on phytopathogenic spores of Fusarium culmorum, Can. J. Microbiol. 56 (3) (2010) 247–253.
[238] C. Dwivedi, C.P. Shah, K. Singh, M. Kumar, P.N. Bajaj, An organic acid-induced synthesis and characterization of selenium nanoparticles, J. Nanotechnol. 2011 (2011) 651971.
[239] R.K. Sharma, R. Ghose, Synthesis of zinc oxide nanoparticles by homogeneous precipitation method and its application in antifungal activity against Candida albicans, Ceram. Int. 41 (1) (2015) 967–975.
[240] M.F. Khan, M. Hameedullah, A.H. Ansari, E. Ahmad, M. Lohani, R.H. Khan, M.M. Alam, W. Khan, F.M. Husain, I. Ahmad, Flower-shaped ZnO nanoparticles synthesized by a novel approach at near-room temperatures with antibacterial and antifungal properties, Int. J. Nanomed. 9 (2014) 853.
[241] A. Sierra-Fernandez, S. De la Rosa-García, L.S. Gomez-Villalba, S. Gómez-Cornelio, M.E. Rabanal, R. Fort, P. Quintana, Synthesis, photocatalytic, and antifungal properties of MgO, ZnO and Zn/Mg oxide nanoparticles for the protection of calcareous stone heritage, ACS Appl. Mater. Interfaces 9 (29) (2017) 24873–24886.
[242] C.M. Magdalane, K. Kaviyarasu, J.J. Vijaya, C. Jayakumar, M. Maaza, B. Jeyaraj, Photocatalytic degradation effect of malachite green and catalytic hydrogenation by UV–illuminated CeO2/CdO multilayered nanoplatelet arrays: investigation of antifungal and antimicrobial activities, J. Photochem. Photobiol. B Biol. 169 (2017) 110–123.
[243] S. Ifuku, Y. Tsukiyama, T. Yukawa, M. Egusa, H. Kaminaka, H. Izawa, M. Morimoto, H. Saimoto, Facile preparation of silver nanoparticles immobilized on chitin nanofiber surfaces to endow antifungal activities, Carbohydr. Polym. 117 (2015) 813–817.
[244] K. Giannousi, G. Sarafidis, S. Mourdikoudis, A. Pantazaki, C. Dendrinou-Samara, Selective synthesis of Cu_2O and Cu/Cu_2O NPs: antifungal activity to yeast Saccharomyces cerevisiae and DNA interaction, Inorg. Chem. 53 (18) (2014) 9657–9666.
[245] E. ISO, 10993-5: Biological evaluation of medical devices, Tests for *in vitro* cytotoxicity (2009).
[246] C.S. Jamieson, J. Misa, Y. Tang, J.M. Billingsley, Biosynthesis and synthetic biology of psychoactive natural products, Chem. Soc. Rev. 50 (2021) 6950–7008.
[247] B.I. Kharisov, H.R. Dias, O.V. Kharissova, A. Vázquez, Y. Pena, I. Gomez, Solubilization, dispersion and stabilization of magnetic nanoparticles in water and non-aqueous solvents: recent trends, RSC Adv. 4 (85) (2014) 45354–45381.
[248] A. Fogden, B. Ninham, Electrostatics of curved fluid membranes: the interplay of direct interactions and fluctuations in charged lamellar phases, Adv. Colloid Interface Sci. 83 (1-3) (1999) 85–110.
[249] M. Madkour, A. Bumajdad, F. Al-Sagheer, To what extent do polymeric stabilizers affect nanoparticles characteristics? Adv. Colloid Interface Sci. 270 (2019) 38–53.
[250] M. Guilger-Casagrande, R.d. Lima, Synthesis of silver nanoparticles mediated by fungi: a review, Front. Bioeng. Biotechnol. 7 (2019) 287.
[251] V. Kathiravan, S. Ravi, S. Ashokkumar, S. Velmurugan, K. Elumalai, C.P. Khatiwada, Green synthesis of silver nanoparticles using Croton sparsiflorus morong leaf extract and their antibacterial and antifungal activities, Spectrochim. Acta Part A 139 (2015) 200–205.
[252] M. Khatami, R. Mehnipor, M.H.S. Poor, G.S. Jouzani, Facile biosynthesis of silver nanoparticles using Descurainia sophia and evaluation of their antibacterial and antifungal properties, J. Clust. Sci. 27 (5) (2016) 1601–1612.
[253] M. Shammout, A. Awwad, A novel route for the synthesis of copper oxide nanoparticles using Bougainvillea plant flowers extract and antifungal activity evaluation, MW Shammout and AM Awwad. A novel route for the synthesis of copper oxide nanoparticles using Bougainvillea plant flowers extract and antifungal activity evaluation, Chem. Int. 7 (1) (2021) 71–78.
[254] K.J. Lee, S.H. Park, M. Govarthanan, P.H. Hwang, Y.S. Seo, M. Cho, W.H. Lee, J.Y. Lee, S. Kamala-Kannan, B.T. Oh, Synthesis of silver nanoparticles using cow milk and their antifungal activity against phytopathogens, Mater. Lett. 105 (2013) 128–131.
[255] B. Chopade, S. Ghosh, S. Patil, M. Ahire, R. Kitture, A. Jabgunde, S. Kale, K. Pardesi, S.S. Cameotra, J. Bellare, Synthesis of silver nanoparticles using Dioscorea bulbifera tuber extract and evaluation of its synergistic potential in combination with antimicrobial agents, Int. J. Nanomed. 7 (2012) 483–496.
[256] S.A. Wadhwani, U.U. Shedbalkar, R. Singh, M.S. Karve, B.A. Chopade, Novel polyhedral gold nanoparticles: green synthesis, optimization and characterization by environmental isolate of Acinetobacter sp. SW30, World J. Microbiol. Biotechnol. 30 (10) (2014) 2723–2731.
[257] M. Shakibaie, A.R. Shahverdi, M.A. Faramarzi, G.R. Hassanzadeh, H.R. Rahimi, O. Sabzevari, Acute and subacute toxicity of novel biogenic selenium nanoparticles in mice, Pharm. Biol. 51 (1) (2013) 58–63.
[258] S. Peng, J.M. McMahon, G.C. Schatz, S.K. Gray, Y. Sun, Reversing the size-dependence of surface plasmon resonances, Proc. Natl. Acad. Sci. 107 (33) (2010) 14530–14534.
[259] D.P. Biswas, N.M. O'Brien-Simpson, E.C. Reynolds, A.J. O'Connor, P.A. Tran, Comparative study of novel *in situ* decorated porous chitosan-selenium scaffolds and porous chitosan-silver scaffolds towards antimicrobial wound dressing application, J. Colloid Interface Sci. 515 (2018) 78–91.
[260] J. Wu, X. Lu, Q. Zhu, J. Zhao, Q. Shen, L. Zhan, W. Ni, Angle-resolved plasmonic properties of single gold nanorod dimers, Nano-Micro Lett. 6 (4) (2014) 372–380.
[261] M. Thiele, J.Z.E. Soh, A. Knauer, D. Malsch, O. Stranik, R. Mueller, A. Csaki, T. Henkel, J.M. Koehler, W. Fritzsche, Gold nanocubes–direct comparison of synthesis approaches reveals the need for a microfluidic synthesis setup for a high reproducibility, Chem. Eng. J. 288 (2016) 432–440.
[262] C. Li, K.L. Shuford, M. Chen, E.J. Lee, S.O. Cho, A facile polyol route to uniform gold octahedra with tailorable size and their optical properties, ACS Nano 2 (9) (2008) 1760–1769.
[263] M. Benkovičová, Z. Kisová, M. Bučková, E. Majková, P. Šiffalovič, D. Pangallo, The antifungal properties of super-hydrophobic nanoparticles and essential oils on different material surfaces, Coatings 9 (3) (2019) 176.
[264] L.S. Wang, A. Gupta, V.M. Rotello, Nanomaterials for the treatment of bacterial biofilms, ACS Infect. Dis. 2 (1) (2016) 3–4.
[265] D.F. Moyano, V.M. Rotello, Nano meets biology: structure and function at the nanoparticle interface, Langmuir 27 (17) (2011) 10376–10385.
[266] N. Bellotti, R. Romagnoli, C. Quintero, C. Domínguez-Wong, F. Ruiz, C. Deyá, Nanoparticles as antifungal additives for indoor water borne paints, Prog. Org. Coat. 86 (2015) 33–40.
[267] A.W.A. Ismail, N.M. Sidkey, R.A. Arafa, R.M. Fathy, A.I. El-Batal, Evaluation of *in vitro* antifungal activity of silver and selenium nanoparticles against Alternaria solani caused early blight disease on potato, Br. Biotechnol. J. 12 (3) (2016) 1.
[268] P. AshaRani, G. Low Kah Mun, M.P. Hande, S. Valiyaveettil, Cytotoxicity and genotoxicity of silver nanoparticles in human cells, ACS Nano 3 (2) (2008) 279–290.
[269] P.L. Drake, K.J. Hazelwood, Exposure-related health effects of silver and silver compounds: a review, Ann. Occup. Hyg. 49 (7) (2005) 575–585.
[270] M. Trop, M. Novak, S. Rodl, B. Hellbom, W. Kroell, W. Goessler, Silver-coated dressing acticoat caused raised liver enzymes and argyria-like symptoms in burn patient, J. Trauma Acute Care Surg. 60 (3) (2006) 648–652.
[271] E.J. Park, E. Bae, J. Yi, Y. Kim, K. Choi, S.H. Lee, J. Yoon, B.C. Lee, K. Park, Repeated-dose toxicity and inflammatory responses in mice by oral administration of silver nanoparticles, Environ. Toxicol. Pharmacol. 30 (2) (2010) 162–168.
[272] T. Wang, X. Chen, X. Long, Z. Liu, S. Yan, Copper nanoparticles and copper sulphate induced cytotoxicity in hepatocyte primary cultures of Epinephelus coioides, PLoS One 11 (2) (2016) e0149484.
[273] L. Yien, N.M. Zin, A. Sarwar, H. Katas, Antifungal activity of chitosan nanoparticles and correlation with their physical properties, Int. J. Biomater. 2012 (2012) 632698.
[274] P. Wayne, Clinical and laboratory standards institute. Performance standards for antimicrobial susceptibility testing, (2011).