

**Novel Strategies Against Fungal Infections: Repurposing Existing Drugs and Advancing
Nanotherapeutics**

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Abstract:

Fungal infections are rising globally, affecting nearly a quarter of the world's population. Driven by growing immunocompromised populations, the overuse of broad-spectrum antibiotics, and the emergence of multidrug-resistant fungi, conventional antifungal agents now face significant challenges in terms of efficacy, toxicity, and resistance. This review highlights emerging antifungal strategies, focusing on drug repurposing and nanomaterial-based approaches, in response to the growing challenge of fungal infections. Drug repurposing has revealed that numerous non-antifungal agents exhibited intrinsic antifungal activity or exerted strong synergistic effects combined with conventional antifungal drugs, thereby expanding the therapeutic pipeline without requiring de novo drug discovery. Meanwhile, advanced polymeric and metallic nanomaterials offer key benefits, such as enhanced drug solubility, targeted delivery, improved biofilm penetration, multimodal fungicidal mechanisms, reduced host toxicity, and a lower propensity to induce resistance. Although most current studies remain preclinical, the convergent advances in drug repurposing and nano-enabled antifungal technologies establish a promising route toward safer, more effective, and resistance-refractory therapies, underscoring the need for continued interdisciplinary innovation to accelerate clinical translation.

Keywords: Fungal infection, Drug repurposing, Polymers, Metal nanoparticles

1. Introduction

Fungal infections represent a pervasive and escalating global health challenge, affecting an estimated quarter of the world's population. While the majority of these are non-life-threatening superficial mycoses affecting the skin, hair, nails, and mucosa, they nonetheless pose a significant clinical burden due to their high prevalence, transmissibility, and tendency to become chronic.¹ More severely, the past decades have witnessed a dramatic increase in life-threatening invasive fungal infections (IFIs), fueled by growing populations of immunocompromised individuals, extensive use of broad-spectrum antibiotics, and advances in critical care. These IFIs now account for over 6.5 million cases and more than 2 million deaths annually, with mortality rates often exceeding 40%—a death toll that surpasses that of tuberculosis or malaria.²⁻⁴ The predominant pathogens of IFIs include *Candida* species, *Aspergillus* species, *Cryptococcus* species, and *Mucorales*.¹⁻⁴ The clinical management of fungal diseases is confronted by a dual crisis: the expanding threat of resistant pathogens and the severe

limitations of existing therapies. The epidemiological landscape is shifting, with a marked rise in infections caused by non-*C.albicans* species and the emergence of multidrug-resistant strains, most notably *Candida auris*.⁵ This pathogen demonstrates alarming pan-resistance to all major antifungal classes, prompting its designation as an "urgent threat" by the CDC and a "critical priority" by the WHO.^{6, 7} Concurrently, azole-resistant *Aspergillus* species and other rare molds are becoming more common, further complicating treatment paradigms.¹ The clinical arsenal against fungal infections is critically limited. The four main systemic antifungal drug classes—polyenes, azoles, echinocandins, and flucytosine—face significant challenges. These include inherent and acquired resistance, poor solubility, rapid clearance, inadequate tissue targeting leading to systemic toxicity (e.g., nephrotoxicity), and the formidable ability of fungi to form biofilms or persist within host cells, evading both drug and immune responses.⁸ The stark contradiction between the escalating burden of fungal disease and the constrained, imperfect therapeutic toolbox highlights an urgent and unmet need for innovative antifungal strategies.

It is within this pressing context that this review explores promising new frontiers in antifungal therapy. We will focus on two key approaches: the repurposing of existing drugs to uncover new antifungal applications, the development of nano-antifungal materials including polymeric and metal nanomaterials. These novel paradigms hold significant potential to overcome the limitations of conventional antifungals, combat resistance, and usher in a new era of effective treatment.

2. Drug repurposing strategies

The process of de novo drug discovery and development, although currently the most common choice for drug development, is time-consuming and expensive, with high attrition rates. In contrast, drug repurposing, referring to the identification of new uses for established medications and abandoned or failed compounds, has emerged as an expedited alternative approach to find new indications for existing drugs.^{9,10} This approach offers many benefits over de novo drug development. The average new drug development time savings has been estimated to reach 5-7 years, and the failure rate for problems related to safety or toxicity is less than 50%. Drug repurposing strategy can substantially decrease the time, effort, and cost that it takes to find a new therapeutic indication and bring rapid benefit to the patients. Compared with the development of new drugs, drug repurposing has several advantages, as mainly reflected in decreased cost and safety risk.^{9,10}

In this chapter, we reported on non-antifungal agents that have been found to be active *in vitro* or even *in vivo* against pathogenic fungi, according to their initial therapeutic class, including antibacterial agents, antiparasitic agents, antiviral agents, immunosuppressants, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, anti-inflammatory drugs, antipsychotic drugs, anticancer drugs, antiarrhythmic drugs and others. The mechanisms of these agents involved cell membrane, vacuole, ribosome, efflux pump, mitochondria, hyphae formation, apoptosis, nucleus, ions channels and cell wall (Figure 1). The synergism effects of non-antifungals and antifungal agents were also summarized since parts of non-antifungals alone showed limited antifungal activities.

2.1 Antibacterial agents

The antifungal activities and mechanisms of antibacterial drugs were widely studied, which mainly include aminoglycosides, macrolides, fluoroquinolones, tetracyclines, polymyxins, tigecycline, rifampicin and linezolid (Table 1).

Aminoglycosides (tobramycin, gentamicin) and macrolides (azithromycin, clarithromycin and ect) mainly inhibited fungal growth at high concentrations. Gentamicin enhanced the efficacy of fluconazole (FLC) against resistant *Candida albicans* via suppressing efflux pump and phospholipase activity.¹⁰ Clarithromycin synergizes with amphotericin B or anidulafungin against biofilm of *C. albicans*, *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*.^{10,11,12} While azithromycin plus amphotericin B (AMB) acted synergistically against *Cryptococcus neoformans*.¹¹ Meantime, tobramycin and azithromycin combined with antifungals showed synergistic effect against filamentous fungi^{10,11}

Most fluoroquinolones exhibited standalone antifungal activity but acted synergistically with antifungals against *Candida* spp, *C. neoformans*, *Aspergillus fumigatus* and *Fusarium* spp *in vitro*.^{10,11,13} Moxifloxacin (MXF) showed relatively low minimum inhibitory concentration (MIC) against planktonic *C. albicans* and acted synergistically with liposomal AMB or caspofungin (CAS); this synergy likely arose from alteration of cell membrane permeability and increase of intracellular MXF levels, enabling inhibition of fungal topoisomerase II.^{10,11,13,14} MXF also inhibited *C. albicans* biofilm formation and the anti-*C. albicans* activity was related to inhibition of yeast-hyphae transition and arresting the cell cycle at S phase.¹⁴ The combination of MXF and antifungals showed synergistic effects against *Fusarium* spp.^{11,15}

For tetracyclines, doxycycline (DOX) and minocycline (MIN) both inhibited *C. albicans* biofilms *in*

vitro at elevated concentrations.^{10,11} DOX plus FLC synergistically inhibited *C. albicans* biofilm formation by inhibition of FLC-inducible efflux pump gene over expression, disturbing calcium and iron homeostasis, inducing apoptosis.^{11,16-30} MIN combined with AMB or azoles acted synergistically against *C. albicans* *in vitro* and *in vivo* via calcium homeostasis disruption, apoptosis and Ras/cAMP pathway inhibition.^{10,19,21,22} For non-*C. albicans* species, both drugs exhibited synergistic activities with antifungals.^{10,11,20,22-24} It was noteworthy that combinations of MIN and other antifungal agents were effective against emerging fungi *Candida auris* *in vitro* and *in vivo*.^{22,24} High synergism (>75%) against *C. neoformans* was observed for the combinations, MIN+AMB.²⁵ For filamentous fungi, DOX plus AMB or azoles synergistically inhibited *Fusarium* species growth.¹⁵ While MIN alone could exhibit antifungal activity against *Aspergillus* spp and *Fusarium* spp with MICs in the range of 0.125-4 µg/mL.¹⁰ In addition, MIN synergized with azoles against *Aspergillus* spp, *Fusarium* spp, *Scedosporium* spp and *Lomentospora prolificans*.^{10, 26}

Polymyxin B (PMB), tigecycline (TGC), rifampicin (RIF) and linezolid were synergistic with antifungals against *Candida* spp and *C. neoformans*.^{10,11,12,24,25,27} For filamentous fungi, PMB, TGC and RIF combined with AMB or azoles showed synergism against *Fusarium* species. Similar results were observed in PMB or RIF combined with antifungals against *Aspergillus* spp.^{10,11} Their antifungal effects involved cell membrane influence and inhibition of protein or RNA synthesis.^{10,11,27}

Among these agents, only MXF, DOX and MIN have undergone limited mechanistic investigation; their precise antifungal mechanisms remain unclear and require further study. Meantime antibacterial treatment could reduce the composition of colonizing microbiota, which disrupts the microbiota balance. Moreover, many antibacterial agents can promote fungal growth and enhance fungal pathogenicity indirectly by disrupting the microbiome and eliminating anaerobic bacteria. Moreover, dysbiosis of microbiota is linked to cardiovascular diseases, cancer, allergy, immune dysfunction and impaired nutrients synthesis. In addition, the pharmacokinetics of antibacterial agents with antifungal activity *in vivo* require further investigation.¹⁰

2.2 Antiparasitic agents

Antiparasitic agents are used to treat infections by a diverse group of organisms encompassing the unicellular protozoas. Here, we reviewed the antifungal use and mechanisms of pentamidine (PNT), chloroquine (CLQ), clioquinol(CQ), miltefosine (MFS) and others (Table 2).

Pentamidine (PNT) alone showed *in vitro* activities against *Candida* spp, *C. neoformans*, *L. prolificans*, *Sporothrix schenckii*, *Aspergillus terreus* and *Fusarium* spp.^{11,28-30} PNT plus auranofin acted synergistically against *C. albicans* and *C. auris* by influencing cell membrane permeability and mitochondrial function.^{11,28,29} PNT also synergized with AMB or azoles against *Fusarium* species¹¹ and dimorphic fungi *S. schenckii*.⁴⁰

Emerging resistance to chloroquine (CLQ) has posed a limitation on its antimalarial use. CLQ showed *in vitro* and *in vivo* antifungal activities against *C. neoformans* by forming iron complexes that induced fungal death in infected macrophages.^{11,31} CLQ enhanced efficacy of FLC or voriconazole (VRC) against *C. albicans* mature biofilms.¹¹

Clioquinol (CQ) was widely used as antibacterial and antiparasitic agents, which also inhibited the growth of common pathogenic fungi with relative low MICs, including *Candida* spp, dermatophytes, *Fusarium* spp and others.³²⁻³⁹ CQ alone exhibited fungistatic and fungicidal activity against *C. albicans*.³⁷ It could influence cell wall, inhibit yeast-hyphae transition and biofilm formation, induce G2/M cell cycle arrest, disturb ion homeostasis, attenuate virulence factors and induce apoptosis to exhibit the antifungal activity.^{34,36,37} Synergistic effects were reported when CQ was combined with antifungals against isolates of *C. auris* (CQ + posaconazole),³⁸ dermatophytes (CQ + terbinafine or ciclopirox),³⁵ *Fusarium* spp (CQ + terbinafine or VRC).³⁹

Miltefosine (MFS), an alkyl phosphocholine used for leishmaniasis and breast tumour, exhibited broad-spectrum antifungal activities against pathogenic fungi, including *Candida* spp, *Cryptococcus* spp, Dermatophytes, dimorphic fungi, *Aspergillus* spp, *Fusarium* spp and etc.^{11,40-44} In addition, MFS's inhibitory and fungicidal effects were demonstrated even against resistant fungal species, such as FLC-resistant *Candida* spp., azoles and echinocandin-resistant *Fusarium* spp., terbinafine-resistant dermatophyte species, *C. auris*, *Scedosporium* spp...^{40,41} It synergized with AMB against *C. auris*, inhibited biofilm formation and/or mature biofilm in *C. albicans*, *C. auris*, *Sporothrix* spp., *Fusarium* spp, *Scedosporium* spp, *L. prolificans*.^{11,40,41} As *in vivo* study, MFS showed effective in *Candida* spp, *Aspergillus* spp and *Cryptococcus* spp. infection models.⁴¹ However, the mechanism of action of MFS on fungi remains poorly understood. The main effect described in fungal cells is the loss of plasma membrane integrity and permeability. The subinhibitory concentration decreased the total ergosterol content.⁴¹ MFS also induced multiple alterations in fungal cells, such as leakage of cytoplasmic content, mitochondrial disturbances, DNA damage, ROS accumulation and apoptosis inducement.⁴¹⁻⁴³ It also

inhibited phospholipase B in *C. neoformans* and melanin accumulation in *Sporothrix brasiliensis* and *Paracoccidioides* spp.^{41,44} In addition to the involvement of sphingolipids in the action of MFS against *A. fumigatus*, it induced mitochondrial fragmentation and necrotic-like cell death in *A. fumigatus*.^{41,43}

The benzimidazoles, artemisinins, niclosamide and tafenoquine exhibited antifungal activities against *Cryptococcus* spp, *Candida* spp and *C. neoformans*, *S. brasiliensis* and *Candida haemulonii* sensu stricto (an AMB-resistant strain), respectively.^{31,45-47} Mechanistic investigation revealed that artemisinins might enhance azoles efficacy through disrupting of the drug efflux pump.⁴⁵

Among the antiparasitic agents, CQ and MFS alone showed good antifungal activities against most pathogenic fungi with low MICs values *in vitro*, few works described its effectiveness *in vivo*. The subacute myelo-optico neuropathy may be related to the use of CQ limits its use.^{37,38} And the main limitation in applying MFS as an antifungal is its potential toxicity to the host, depending on the dose administered. Modifying MFS formulations can reduce such toxic effects.⁴¹ Mentime, the antifungal mechanisms of CQ and MFS are not fully understood. The FDA granted orphan drug designation for using MFS to treat invasive candidiasis in the USA, emphasizing the need to develop more research and clinical trials for MFS repositioning as antifungal therapy.⁴¹

2.3 Antiviral agents

,The HIV protease inhibitor lopinavir enhanced the antifungal activity of itraconazole (ITR) against *Candida* species, including *C. auris*.⁴⁸ The purine nucleoside analogues ribavirin and vidarabine showed antifungal effects: ribavirin exhibited fungistatic activity against drug-resistant *C. albicans* and fungicidal activity against *C. parapsilosis*, synergized with AMB, FLC or ITR against drug-resistant *C. albicans*,³¹ vidarabine synergized with antifungals against *C. albicans* *in vivo* and *in vitro* by targeting ergosterol synthesis, increasing intracellular ROS, and inducing apoptosis.⁴⁹ The antifungal activities of antiviral agents alone were limited with possible adverse effects, requiring further *in vivo* studies for clinical validation.

2.4 Immunosuppressants

The immunosuppressants mainly include calcineurin inhibitors (e.g., cyclosporine, CsA; tacrolimus, FK506), target of rapamycin inhibitors (e.g., rapamycin), antimetabolic agents, and etc. Initially, rapamycin inhibited growth of *C. albicans*, *C. neoformans*, dermatophytes, *Mucor* spp, *Aspergillus* spp.

¹⁰ CsA and FK506 showed activities against *C. neoformans*. Synergism was shown when FK506 was combined with FLC and with CAS against *C. neoformans*. When tested *in vitro* against *C. parapsilosis*, CsA presented synergistic interactions with AMB, azoles and CAS. Similarly, CsA interacted synergistically *in vitro* against *C. albicans*. and inhibition of *C. albicans* biofilms by FLC was enhanced. Together, CsA and FK506 interacted synergistically with FLC, ITR or AMB against *C. glabrata*, although CsA and FK506 alone had not shown any activity against this fungus. FK506 alone inhibited *A. fumigatus* growth and synergism was seen when it was combined with CAS or VRC *in vitro* against *A. fumigatus*.¹¹ Their mechanisms remain unclear, and structural modification is needed to lower immunosuppressive side effects.

2.5 HMG-CoA reductase inhibitors

Statins are 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors limiting velocity of cholesterol synthesis, which are primarily used in the treatment of hyperlipidemia. Parts of these (fluvastatin, simvastatin, atorvastatin, pitavastatin) also have antifungal activities. The mechanism of antifungal action of statins in combination with antifungal agents is still unclear. It has been hypothesised that the inhibition of HMG-CoA reductase could lead to a decrease of ergosterol levels or another cytosolic precursor of ergosterol required in the fungal cell membrane synthesis.¹¹ While the *in vivo* studies of statins were limited.

For yeast, fluvastatin (FVS), simvastatin (SIM) and atorvastatin inhibited *Candida* spp growth *in vitro*. The combination of FVS/SIM with azoles yielded synergism in *Candida* spp.^{10,11,51} In a randomized, double-blind controlled trial demonstrated that atorvastatin was effective in reducing *Candida* species in participants with denture stomatitis.⁵² SIM and atorvastatin also showed inhibitory effects against isolates of *Cryptococcus* spp *in vitro*. The combination of SIM with azoles or AMB was synergistic in *Cryptococcus* spp.^{10,11} FVS increased the effect of CAS against *A. fumigatus* *in vitro*. Meanwhile, significant effect of FVS in combination with azoles against *A. fumigatus* and *Aspergillus flavus* was reported. Pitavastatin (PIT) and ITR combination exhibited significant synergistic antifungal activity against *Aspergillus* spp *in vitro* and *in vivo*.⁵⁰ Atorvastatin also inhibited *Aspergillus* spp growth.^{10,51} Only FVS showed synergism against *Fusarium* species was shown in combinations with AMB and VRC *in vitro*.^{10,11}

2.6 Anti-inflammatory Drugs

Non-steroidal anti-inflammatory agents (NSAIDs) are primarily analgesic, and antipyretic compounds that inhibit cyclooxygenase enzymes and reduce the synthesis of prostaglandin in mammals, including acetylsalicylic acid (ASA), nimesulide (NIM), ibuprofen (IBP) and etc. Auranofin and theophylline (THP) also showed anti-inflammatory activities. Meantime, these drugs exhibited antifungal activities *in vitro* and *in vivo*.

ASA alone inhibited planktonic cells and biofilms of *Candida* spp *in vitro*. However, only high concentrations were able to inhibit the growth of *C. auris* and FLC-resistant *C. albicans* strains and their biofilms *in vitro*. It synergized with AMB or FLC against *Candida* spp and its biofilm. The ASA could reduce tissue damage in infection models of *C. albicans* and *C. parapsilosis*.¹¹ High-dose ASA also inhibited growth of *Cryptococcus* species *in vitro*. NIM partially inhibited *C. albicans* biofilm formation and acted against *Cryptococcus* spp and *A. fumigatus* at high concentration *in vitro*.¹¹ For IBP, it showed activity against *C. albicans* and *Cryptococcus* species growth, synergized with antifungals against multiple fungi, including *Cryptococcus* spp., *Candida* spp., *Fusarium* spp.^{11,31} The fungicidal activity of IBP at high doses via direct damage of the cytoplasmic membrane. Concentrations of IBP that kill *Candida* cells induced a quick and extensive potassium efflux, indicating that killing by IBP is caused by direct damage to the cell membrane.¹¹

Auranofin inhibits several inflammatory pathways and has been used as an antirheumatic drug, which also displayed an activity against various yeast and molds such as *C. albicans*, *C. neoformans*, *A. fumigatus*, *Scedosporium apiospermum* and *L. prolificans* at relatively low concentrations. The mechanism was related to action on reactive-oxygen-mediated cell death.³¹

THP belongs to the methylxanthine class of drugs and has known anti-inflammatory properties, which is generally used for asthma or chronic obstructive pulmonary disease. It inhibited the growth of *Candida* species at low concentrations. Mechanistic insights of *C. albicans* revealed that THP induced membrane damage. Enhanced ionic disturbances and depleted ergosterol levels with the concomitant rise in membrane fluidity due to elevated flippase activity confirmed the membrane damaging effect. THP impeded the metabolic adaptability by inhibiting enzymes in the glyoxylate cycle. *In vivo* efficacy of THP was depicted by increased survival of *C. albicans* infected *Caenorhabditis elegans* model.^{31,53}

2.7 Antipsychotics and antidepressant drugs

Fungal infections affecting the brain have poor prognoses. It is critical to develop antifungals that can penetrate the central nervous system (CNS) and clear the fungal burden in the brain. The antipsychotic and antidepressant agents' effects on CNS to exhibit its activities in treatment and exhibited antifungal activities. The mechanism studies were also summarized (Table 3).

Haloperidol, trifluoperidol, phenothiazines (chlorpromazine, CLOR; trifluoperazine, TRI) block the central dopamine D2 receptor to improve symptoms in mentally ill patients, which exhibited the growth of *Candida* spp and *C. neoformans*. Haloperidol and trifluoperidol alone inhibited the growth of *C. albicans* or *C. neoformans* in low concentrations while CLOR and TRI alone showed limited antifungal activity. Meantime, all four drugs synergized with azoles against yeast.^{10,31} As for mechanistic insights against *C. albicans*, haloperidol and trifluoperidol had a similar effect to FLC, acting on the yeast membrane (possible action on G protein-coupled receptors).³¹ For filamentous fungi, CLOR and TRI were active *in vitro* against *Aspergillus* spp and *Scedosporium* species.^{10,11,31} However, clinical use is limited by high side effects and non-specific eukaryotic toxicity.¹¹

There are currently various antidepressant drugs used in clinics, including monoamine oxidase inhibitors, tricyclic, tetracyclic, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitor (NRIs) and etc. Encouragingly, SSRIs have been shown to have positive antifungal activity in various studies, such as sertraline (SERT).

SERT exerted fungicidal activity against *C. neoformans* with low MICs *in vitro* and reduced fungal burden in murine models of cryptococcosis, while synergizing with azoles or AMB against various *Cryptococcus* spp.^{11,31} However, the results of clinical trials of SERT for infectious diseases were disappointing. In 2019, a clinical trial demonstrated that SERT did not reduce mortality and should not be used to treat patients with HIV-associated cryptococcal meningitis.⁵⁴ In 2020, another randomized trial testing SERT as pre-emptive therapy was stopped without a final conclusion due to the severe side effects of SERT that were observed.⁵⁵ The mechanism for the anti-*Cryptococcus* spp activity was attributed to non-specific cytotoxicity due to its lipophilic nature.¹¹ The membrane organisation and vesicle-mediated transport as its antifungal targets. Moreover, the broad antiproliferation activity of SERT might interfere with translation, leading to inhibition of protein synthesis.

It also showed fungicidal activity against *Candida* spp. *in vitro*, including *C. auris*.⁵⁶⁻⁵⁸ It inhibited both mature and forming biofilms of different *Candida* species.⁵⁹ Synergistic effects were reported when SERT was combined with azoles against isolates of *Candida* spp. The anti-*Candida* spp

mechanism was related to cell membrane and wall inhibition, inducing apoptosis, blocking active efflux pumps.⁵⁶⁻⁵⁸ For filamentous fungi, SERT showed fungicidal activity against *Aspergillus* spp.¹¹ It alone or combined with CAS showed antifungal activity against *Trichophyton rubrum*.^{60,61}

Reboxetine is one of NRIs and the combinations of Reboxetine and FLC or ITR showed anti-*Candida* activities.⁶² The tricyclic antidepressants (TCAs) also showed antifungal activities. Amitriptyline, nortriptyline and clomipramine isolated and associated with AMB inhibited *Candida* spp growth via the apoptotic pathway.⁶³ The *in vitro* study of antidepressant drugs showed encouraging results while the clinical studies results were not satisfactory.

2.8 Anticancer drugs

Anticancer drugs often work on the basic metabolism pathways of eucaryotic and human cells such as the DNA replicating pathway, yeast cells may also be affected. Various anticancer drugs have been seen to be efficient against fungal growth and the mechanism studies were also summarized (Table 4).

Tamoxifen and toremifene, estrogenic receptor antagonists, exerted fungicidal activity against *C. neoformans* in macrophages and inhibited *C. albicans*. Tamoxifen induced cell lysis and an alteration of fungal development. The interaction between tamoxifen and its target NADPH-Cytochrome P450 reductase Ccr1 has also been described as causing the disruption of cell wall integrity. Both compounds synergized *in vitro* with AMB and FLC against cryptococcal cells. However, a clinical trial of tamoxifen combined with AMB and FLC for cryptococcal meningitis demonstrated high-dose tamoxifen does not increase the clearance rate of *Cryptococcus* from cerebrospinal fluid.³¹

Ponatinib is an oral tyrosine kinase inhibitor and has been evaluated to impede tumour progression, including tumors in thyroid, breast, ovary and lung, neuroblastoma and others. It synergized broadly with FLC against *C. albicans* and *C. neoformans* by reducing FLC efflux via Pdr5 and inhibiting proton pump Pma1 expression.⁶⁴

Everolimus, a rapamycin (TOR) inhibitor, was used for treatment of renal cell carcinoma, pancreatic neuroendocrine tumors and etc. The TOR might play an important role in various physiological functions of pathogenic fungi, such as nutrient sensing, stress response, and cell cycle progression. Everolimus alone inhibited the growth of *Aspergillus* spp, *Exophiala* spp., *Phialophora* spp, *Fonsecaea* spp at relative high concentrations⁶⁵⁻⁶⁷ and *C. neoformans* at relatively low concentrations.⁶⁸ It acted synergistically with AMB or azoles against *Exophiala dermatitidis* *in vivo* and *in vitro*, potentially due

to the induction of ROS activity and inhibition of efflux pump.⁶⁷ Synergy was observed between everolimus and antifungals (AMB or azoles) against *Aspergillus* spp and *C. neoformans*.^{65,66,68}

Carmofur can influence DNA, RNA, and protein synthesis, which is mainly used in gastrointestinal cancer. It alone or combined with antifungals showed antifungal activities against dematiaceous fungi. Synergistic effects were reported when carmofur was combined with antifungals against isolates of *Exophiala heteromorpha*, *Fonsecaea pedrosoi*, *Fonsecaea monophora* and *Fonsecaea nubica* (carmofur + ITR or AMB), *Phialophora verrucosa* (carmofur + ITR).⁶⁹

However, administration of anticancer molecules to patients who are often immunocompromised should only be taken after careful consideration due to the numerous side effects that these compounds can cause, including immunosuppression.

2.9 Antiarrhythmic drugs

Antiarrhythmic drugs, which are used in the prevention and treatment of tachycardia, bradycardia, or arrhythmia, such as β -receptor blockers, potassium channel blockers (PCRs), calcium channel blockers (CCBs).¹⁰ CCBs, prevent calcium ions from entering cells and maintain metabolic processes.

Verapamil (VER), a phenylalkylamine CCB, mainly combated *C. albicans* by affecting hyphae development, adhesion, or increasing strain susceptibility to oxidative stress. It also enhanced the antifungal activity of FLC against *C. albicans* during biofilm formation and preformed biofilms.¹⁰ The VER alone exhibited antifungal activity against *C. neoformans* at high concentration. The combination of VER and AMB/CAS exhibited synergism.^{70,71} Mechanistically, VER reduced chitosan content and disrupted cell wall integrity. VER+CAS modified membrane permeability, triggering intracellular ROS accumulation and mitochondrial membrane potential alterations. VER mitigated CAS-induced calcium fluctuations, downregulated calcineurin pathway genes and influenced chitin deacetylase activity.⁷¹ In *A. fumigatus*, the drug efflux pump was blocked and ergosterol content was decreased following treatment with verapamil and itraconazole simultaneously.¹⁰ High-dose amlodipine showed fungicidal activity against *S. brasiliensis* and displayed partial synergy. with ITR against clinical isolates.⁷²

Other CCBs, such as diltiazem, nifedipine, and nifedipine, exerted antifungal activity alone or combined with antifungals against *C. albicans*, *C. glabrata* and *Mucor* fungi.¹⁰ Amiodarone is known to block potassium, sodium, and calcium channels. Amiodarone mainly disrupted calcium homeostasis to elicit high levels of cytoplasmic calcium, leading to cell death in *Candida* spp, *Cryptococcus* spp.,

Aspergillus spp., *Fusarium oxysporum*. In addition, amiodarone displayed potent fungicidal effects at a low dose combined with FLC and miconazole.¹⁰ Hence, calcium channels may be potential targets in the therapy of fungal-related infections while more *in vivo* evidences needed.

2.10 Other approved drugs

Astemizole (AST) is a second-generation selective histamine H1-receptor antagonist used to treat seasonal allergic rhinitis, which could cross the blood-brain barrier. AST plus FLC showed antifungal activity against *Cryptococcus* spp *in vitro* and *in vivo*, but not when they were challenged with a FLC-resistant strain of *C. neoformans*. The main objection to the use this combination is that AST can cause a rare complication leading to arrhythmias in few patients.¹¹

Disulfiram is an alcohol antagonist drug, which inhibited FLC-sensitive and resistant yeast strains growth, with an inhibiting effect on biofilm formation. It also had a fungicidal activity on *Aspergillus* spp. It could reverse Cdr1p-mediated drug resistance so it could be used in combination to sensitize resistant strains.³¹

Teriflunomide is used for treatment of multiple sclerosis. The combination of teriflunomide and FLC has a significant synergistic effect in all resistant *C. albicans* isolates *in vitro* and *in vivo*. Also, this drug combination could inhibit the immature biofilm biomass and hyphae formation.⁷³

Zoledronate (ZOL) is widely used for osteoporosis treatment, exhibited antifungal activities against *Candida* spp, *Cryptococcus* spp, Dermatophytes at high concentrations. ZOL also synergized with antifungals against isolates of *Candida* spp and *Cryptococcus* spp, Dermatophytes, *Aspergillus* spp and *Mucor* spp. The inhibitory effects of ZOL alone and in combination with other azoles in *Trichophyton rubrum* were due to the inhibition of squalene synthesis and increase of oxidative stress.⁷⁴

Otilonium bromide (OTB), which has a selective antispasmodic effect on smooth muscles and is used to treat irritable bowel syndrome. It exhibited broad-spectrum antifungal properties against *Candida* species *in vitro* and *in vivo*. Mechanistically, OTB impairs vesicle-mediated trafficking in *C. albicans* by targeting Sec31, thereby impeding the plasma membrane localization of the ergosterol transporters. Consequently, OTB obstructed the movement of ergosterol across membranes and triggered cytotoxic autophagy. It is noteworthy that *C. albicans* encounters challenges in developing resistance to OTB because it is not a substrate for drug transporters.⁷⁵

Firsocostat is a human acetyl-CoA carboxylase (ACC) inhibitor and has been tested in several

clinical trials for the treatment of non-alcoholic steatohepatitis. Firsocostat alone displayed moderate antifungal activity against *C. albicans*, while combining it with azoles or AMB exhibited synergistic effects across almost all drug-sensitive and drug-resistant *C. albicans* strains tested *in vitro* and *in vivo*. It was shown to directly bind to *C. albicans* ACC and inhibit its enzymatic activity.⁷⁶

3. Nanomaterial-based antifungal strategies

Nanotechnology demonstrates tremendous potential in the field of antifungal therapy, particularly in addressing the growing problem of fungal drug resistance. In recent years, antifungal polymeric nanomaterials and metallic nanoparticles have emerged as research hotspots.⁷⁷⁻⁷⁹ On one hand, these nanomaterials can serve as drug delivery carriers, improving the water solubility, stability, and targeting specificity of conventional antifungal drugs through encapsulation, conjugation, or surface modification, thereby reducing their toxicity and side effects. Furthermore, both the two nanomaterials possess intrinsic antifungal activity.⁷⁷⁻⁷⁸ Benefiting from advanced synthesis and characterization techniques, researchers can precisely tailor the molecular structure, charge density, and hydrophilicity-lipophilicity balance of polymers and metallic nanoparticles to optimize their antifungal activity and biocompatibility. Polymeric nanomaterials included liposomes, micelles, cyclodextrins, and dendrimers, which could be engineered as stealth, pH-sensitive, thermosensitive, or enzyme-responsive systems. Metallic nanoparticles consisted of silver nanoparticles, gold nanoparticles, copper nanoparticles, iron oxide nanoparticles, zinc oxide nanoparticles, titanium dioxide nanoparticles, with various modifications. These multifunctional nanomaterials provided important directions for developing novel antifungal therapies that are highly efficient, low in toxicity, and less prone to inducing resistance (Figure 1).

3.1 Polymeric nanoparticles

Polymeric nanoparticles (PNPs) represent a class of nanoscale drug delivery systems fabricated through the emulsification of biodegradable macromolecular polymers, typically ranging in size from 1 to 1000 nanometers.⁷⁷ Based on their morphological structure and functional characteristics, PNPs can be classified into two main categories.⁷⁸ The first category comprises PNPs designed to enhance the performance of antifungal drugs. These materials do not exhibit intrinsic antifungal activity but instead improve the efficacy of existing antifungal agents through physical or chemical mechanisms, such as

enhancing water solubility, enabling targeted delivery, improving biocompatibility, and promoting therapeutic effects. The second category includes synthetic polymers that possess inherent antifungal activity. These polymers mimic the structural and functional properties of natural antifungal peptides—such as host defense peptides—to develop novel antifungal materials with direct antimicrobial action.

3.1.1 PNPs Enhance the Performance of Existing Antifungal Drugs

Encapsulation of Small-Molecule Drugs in Nanocarriers

Most conventional antifungal agents are small organic molecules, which suffer from poor water solubility, limited tissue penetration, tendency to develop drug resistance, and host toxicity. Encapsulating these drugs into PNPs can significantly improve their local concentration, solubility, stability, and bioavailability, while simultaneously reducing direct contact with host cells to mitigate toxicity. To this end, various polymeric formulations have been investigated, ranging from liposomes,⁷⁸ micelles⁸⁰ to dendrimers⁸¹ and cyclodextrins.⁸²

Liposomes. Liposomes have emerged as a promising nanocarrier system for antifungal drug delivery, offering significant advantages in enhancing the pharmacokinetic profiles and reducing the systemic toxicity of conventional antifungal agents. Composed of a hydrophobic lipid bilayer encapsulating an aqueous core, liposomes typically range from 70 to 150 nm in diameter and exhibit a net negative surface charge.⁸³ They are particularly effective in encapsulating poorly water-soluble and nephrotoxic drugs such as AMB. By sequestering AMB within the lipid bilayer, liposomal formulations minimize nonspecific interactions with mammalian cholesterol, thereby substantially reducing renal and hemolytic toxicities.

The clinically approved formulation AmBisome® exemplifies this strategy, maintaining potent fungicidal activity against a broad spectrum of pathogens—including *Candida*, *Cryptococcus*, and *Aspergillus* species—while demonstrating improved safety.⁸⁴ Notably, intact liposomal nanoparticles can traverse the fungal cell wall and deliver their payload directly to the plasma membrane, enabling targeted antifungal action. Studies confirm that liposome-mediated delivery enhances local drug concentration at infection sites and prolongs circulation time, improving therapeutic efficacy.⁷⁸ Moreover, surface modifications—including PEGylation ("stealth" liposomes) for prolonged circulation and ligand-mediated targeting—enable active delivery to infected tissues, while

stimuli-responsive designs (e.g., pH-sensitive, thermosensitive, thermosensitive magneto- or enzyme-responsive systems) allow for controlled release in pathological microenvironments. These engineered advantages position liposomes as highly effective and adaptable carriers for advancing antifungal treatment strategies, especially in combating resistant or deep-seated fungal infections.⁸⁵

Micelles. Micelles are spherical nanostructures self-assembled from amphiphilic block copolymers, featuring a hydrophilic shell and a hydrophobic core, making them suitable for encapsulating hydrophobic drugs such as AMB) and azoles. Commonly used polymers include polystyrene-block-poly(ethylene glycol) (P(styrene)-b-PEG) and poly(caprolactone)-block-poly(ethylene glycol) (PCL-b-PEG).^{86,87} Studies have shown that reducing micelle size to below 200 nm enhances antifungal efficacy.^{80,88} Furthermore, incorporating pH- or enzyme-responsive polymers enables accelerated drug release in acidic microenvironments, which is particularly advantageous for targeting fungal biofilm infection sites.

Albayaty et al⁸⁹ developed a pH-responsive micellar drug delivery system based on the diblock copolymer P(PEGMA-b-DEAEMA) to enhance the efficacy of ITR against *C. albicans* biofilms. Biofilm formation confers high resistance to antifungal agents, posing a major therapeutic challenge. The micelles exhibited a uniform size of approximately 55 ± 6 nm and achieved high ITR loading ($12.0 \pm 0.5\%$ w/w). Under physiological pH, the micelles remained stable, with the hydrophobic DEAEMA block forming the core. However, in the acidic microenvironment of biofilms (pH ~ 5), protonation of tertiary amines in DEAEMA increased its hydrophilicity, triggering micelle swelling and accelerated drug release. *In vitro* studies demonstrated that ITR-loaded micelles significantly reduced biofilm biomass by over 70% and decreased viable cell counts by 2.4 log units compared to free ITR. Confocal laser scanning microscopy revealed strong affinity and accumulation of the micelles within biofilms, attributed to electrostatic interactions between positively charged micelles and the negatively charged biofilm matrix. Notably, even blank micelles showed intrinsic anti-biofilm activity, likely due to disruption of biofilm architecture. Overall, this pH-responsive micellar system enhanced ITR solubility, enables targeted delivery, and promotes triggered release within biofilms, offering a promising strategy for overcoming biofilm-mediated antifungal resistance.

Uroro et al⁹⁰ reports the development of a lipase-responsive AMB-loaded polycaprolactone (PCL) nanoparticle system for targeted antifungal therapy. The nanoparticles were fabricated using an oil-in-water emulsion solvent evaporation method, enabling on-demand drug release at infection sites.

Since pathogenic fungi such as *C. albicans* secrete high levels of lipase—and PCL is susceptible to lipase degradation—the system selectively releases AMB in the presence of the enzyme while remaining stable under non-enzymatic conditions. In vitro release studies showed that 62% of AMB was released within 72 hours in the presence of lipase, compared to only 13% in its absence. The minimum inhibitory concentration (MIC) of PCL-AMB NPs against *C. albicans* was 0.06 µg/mL, significantly lower than that of free AMB (0.25 µg/mL), indicating enhanced antifungal efficacy. Disk diffusion assays further confirmed superior inhibition zones for the nanoformulation. Cytotoxicity testing revealed that encapsulation markedly reduced AMB-induced toxicity to primary human dermal fibroblasts, with cell viability increasing from 69.1% (free drug) to 80.1% (nanoparticles). In conclusion, this lipase-responsive PCL-based nanocarrier enhances both the potency and biocompatibility of AMB, representing a promising strategy for targeted antifungal treatment.

Cyclodextrins. Cyclodextrins (CDs) are cyclic oligosaccharides composed of 6, 7, or 8 glucose units linked by α -1,4-glycosidic bonds, which are called α , β , γ -cyclodextrin respectively, forming a truncated cone-shaped structure with a hydrophilic outer surface and a hydrophobic inner cavity.⁹¹ This amphiphilic architecture enables CDs to encapsulate hydrophobic guest molecules via non-covalent inclusion complexation, thereby enhancing the aqueous solubility, stability, and bioavailability of poorly water-soluble drugs. In the context of antifungal therapy, cyclodextrins have been extensively investigated as nanocarriers to improve the physicochemical properties of antifungal agents, particularly polyenes and azoles.^{92,93} For instance, epichlorohydrin-cross-linked cyclodextrin loaded with AMB demonstrated potent *in vitro* activity against *Saccharomyces cerevisiae* while exhibiting reduced cytotoxicity toward mouse embryonic fibroblasts compared to the free drug.⁹⁴ Furthermore, conjugation of cyclodextrin with natural polymers such as chitosan has been shown to enhance corneal penetration, improving ocular delivery in a fungal keratitis model.⁹⁵ With over 30 cyclodextrin-based formulations already approved for clinical use, their biocompatibility, low toxicity, and versatile functionalization potential underscore their significance as effective excipients in advanced antifungal drug delivery systems.

Dendrimers. Dendrimers are a class of highly branched, structurally precise, and tunable synthetic macromolecules that have demonstrated significant potential in nanomedicine and drug delivery systems.⁹⁶⁻⁹⁸ Their unique spherical architecture consists of a central core, multiple layers of repeating units (referred to as "generations"), and a high density of surface-exposed functional end groups. This

well-defined structure enables dendrimers to efficiently encapsulate antifungal agents through electrostatic interactions, hydrophobic inclusion, or covalent conjugation, forming stable complexes known as "dendriplexes." Such formulations enhance the water solubility, stability, and targeting capability of the loaded drugs, while enabling controlled and sustained release profiles—thereby improving therapeutic efficacy and reducing systemic toxicity.⁹⁹⁻¹⁰² For instance, poly(amidoamine) (PAMAM) and poly(propylene imine) (PPI) dendrimers have been shown to effectively solubilize poorly water-soluble antifungal agents such as clotrimazole, ITR, and AMB, significantly enhancing their in vitro antifungal activity.¹⁰³⁻¹⁰⁷ Notably, certain dendrimers exhibit intrinsic antifungal activity even in the absence of loaded drugs.

This direct antimicrobial effect is primarily attributed to the electrostatic interaction between the cationic surface groups of the dendrimers and the negatively charged components of fungal cell membranes. This interaction can disrupt membrane integrity via a "carpet model" mechanism, leading to increased permeability and leakage of intracellular contents.¹⁰⁸ Moreover, specific amino acid-based or lipopeptide-modified dendritic structures have been reported to interfere with fungal cell wall biosynthesis by inhibiting key enzymes such as 1,3- β -D-glucan synthase or disrupting chitin assembly, thereby exerting a dual mode of action.^{109,110} Studies have demonstrated that certain poly-L-lysine (PLL)-based dendrimers display potent antifungal activity against various *Candida* species, with minimal inhibitory concentrations (MICs) reaching micromolar levels—comparable or even superior to some conventional antifungal agents.^{111,112} Beyond their roles as drug carriers or direct antimicrobials, dendrimers also play a pivotal role in antimicrobial photodynamic therapy (aPDT). By serving as carriers for photosensitizers (e.g., silicon phthalocyanine Pc4) or by being structurally engineered into photosensitizing dendrimers themselves, they can generate reactive oxygen species upon light irradiation, enabling selective and localized killing of fungal cells.^{113,114} Furthermore, dendrimer-based biosensors have been developed for the detection of mycotoxins such as aflatoxin B1 and ochratoxin A, highlighting their emerging potential in the diagnosis of fungal infections and mycotoxin contamination.¹¹⁵⁻¹¹⁷

Antifungal Drug–Polymer Conjugates

Antifungal drug-polymer conjugates represent a sophisticated strategy to enhance the physicochemical and pharmacological properties of existing antifungal agents.¹¹⁸ These systems

involve the covalent attachment of an active antifungal drug to a hydrophilic or amphiphilic polymer backbone via a biodegradable linker, forming a construct typically composed of three elements: (1) a water-soluble polymer carrier, (2) the conjugated drug, and (3) optionally, a pathogen-targeting moiety for site-specific delivery.¹¹⁹ This approach addresses key limitations such as poor aqueous solubility. For instance, conjugation of AMB to arabinogalactan significantly improved its hydrophilicity and demonstrated superior pharmacokinetic profiles in rats compared to the liposomal formulation AmBisome, including prolonged blood circulation and reduced clearance.^{119,120} To enable localized drug release at infection sites, stimuli-responsive linkers have been developed. pH-sensitive imine bonds, for example, allow controlled release of AMB under acidic conditions typical of fungal microenvironments, while remaining stable at physiological pH, thereby reducing off-target toxicity.^{121,122} Enzymatically cleavable linkers, such as β -glucopyranoside, are designed to be degraded by fungal extracellular enzymes like β -glucosidase, enabling site-specific activation.^{123,124} Furthermore, incorporating natural pathogen-recognition motifs—such as the Dectin-2 receptor—into the conjugate enhances specificity and efficacy against pathogens like *C. albicans*.¹²⁵⁻¹²⁷ These advances demonstrate that rationally engineered drug-polymer conjugates can simultaneously improve drug solubility, stability, and targeting, offering a promising avenue for the next generation of precision antifungal therapies.

3.1.2 Intrinsically antifungal synthetic polymers

Intrinsically antifungal synthetic polymers represent a promising new strategy in the fight against invasive fungal infections. These materials are rationally designed to mimic naturally occurring host defense peptides—specifically antifungal peptides (AFPs), such as human-derived LL-37 and histatin 5, as well as plant-derived NaD1. Natural AFPs typically adopt cationic, amphiphilic structures that enable selective interaction with fungal cell membranes, leading to membrane permeabilization, disruption, or induction of reactive oxygen species, ultimately resulting in fungal cell lysis.¹²⁸⁻¹³² Despite their broad-spectrum activity and low propensity for resistance development, clinical translation of natural antimicrobial peptides has been hindered by several limitations, including susceptibility to proteolytic degradation, high production costs, and off-target cytotoxicity, particularly hemolytic effects.

To overcome these challenges, researchers have developed a new generation of

peptide-mimicking synthetic polymers, including poly(methacrylates),¹³³ polycarbonates,¹³⁴ nylon-3 polymers,¹³⁵ and poly(2-oxazolines).¹³⁶ These synthetic analogues retain key structural and functional features of natural AFPs while offering enhanced stability and tunability. Notably, studies have demonstrated that low molecular weight cationic copolymers (approximately 2500–4500 Da) with a degree of polymerization (X_n) around 20 exhibit an optimal balance between potent antifungal activity and biocompatibility toward mammalian cells. Among various cationic side chains, guanidinium groups—which mimic arginine residues—confer superior antifungal efficacy compared to primary amine functionalities (lysine mimics). Furthermore, strategic incorporation of anionic monomers, such as carboxylic acid-containing units, can effectively reduce nonspecific toxicity to host cells by modulating overall charge density and enhancing selectivity, without significantly compromising antifungal potency.^{137,138}

Recent advances highlight the therapeutic potential of advanced polymer architectures. For instance, guanidinium-functionalized poly(2-oxazolines) with short spacer lengths have demonstrated exceptional *in vitro* activity against diverse *Candida* and *Cryptococcus* species. Remarkably, these polymers not only maintain efficacy *in vivo* but also exhibit blood-brain barrier-penetrating capability, enabling significant reduction of fungal burden in both systemic infection and fungal meningitis mouse models.¹³⁶ This dual functionality positions them as promising candidates for treating deep-seated and central nervous system-associated fungal infections.

Beyond static antimicrobial action, emerging strategies focus on developing "on-demand" activatable antifungal systems through the integration of stimuli-responsive functional groups. One such approach involves nitric oxide (NO)-releasing polymers, which generate free radicals at the site of infection to synergistically disrupt fungal biofilms and modulate inflammatory responses, thereby promoting wound healing.¹³⁹⁻¹⁴¹ Another innovative avenue is photodynamic therapy (PDT), wherein photosensitizers such as porphyrins, phthalocyanines, hypocrellin, or upconversion nanoparticles are incorporated into polymeric scaffolds. Upon irradiation with specific wavelengths—including near-infrared (NIR) light—these systems produce cytotoxic ROS locally. This approach not only offers potential for the localized treatment of cutaneous and mucosal fungal infections but also holds promise for overcoming the limited tissue penetration associated with conventional phototherapy, thereby facilitating non-invasive management of deep-seated fungal infections.¹⁴²⁻¹⁴⁵

Owing to their tunable physicochemical properties and capacity for multifunctional integration, PNPs have recently emerged as a promising platform that not only addresses key limitations of conventional antifungal therapies but also paves the way toward precise, efficient, and low-toxicity antifungal treatment strategies.

3.2 Antifungal metal nanoparticles

Metal nanoparticles (MNPs) have emerged as a promising strategy for combating drug-resistant fungal infections, owing to their distinctive physicochemical properties, including high specific surface area, tunable size and morphology, and multiple antimicrobial mechanisms.⁷⁹ In recent years, metallic nanoparticles such as silver, gold, and copper have been extensively investigated as novel antifungal agents. These nanoparticles exert potent fungicidal effects against both yeasts and filamentous fungi, including clinical isolates resistant to azoles and echinocandins, through diverse mechanisms such as the release of metal ions, induction of reactive oxygen species burst, disruption of cell membrane integrity, and interference with key intracellular biological processes.⁷⁹ Furthermore, their multi-target mode of action contributes to delaying or circumventing the development of drug resistance. They also demonstrate an enhanced ability to penetrate and inhibit fungal biofilm formation, thereby overcoming the limitations of conventional antifungal agents in the treatment of biofilm-associated infections.¹⁴⁶⁻¹⁵² In this chapter, we reviewed the current research on the antifungal properties of metal-based nanoparticles, covering metals and metal oxides.

3.2.1 Silver nanoparticles (AgNPs)

AgNPs, as the earliest inorganic metal utilized and most widely studied by humans, are widely applied in the field of biomedicine due to their unique physical, chemical and biological intrinsic properties. AgNPs exhibited favorable traceability and permeability within biological systems, allowed for tunable surface functionalization and chemical modification, possessed a high surface-to-volume ratio, and can be synthesized through relatively simple and scalable methods, including biological synthetic, green synthetic, surface-modified, and composite/hybrid approaches. To date, AgNPs have demonstrated significant potential in diverse applications such as drug delivery systems, antimicrobial bacterial and antifungal agents, anticancer and antiviral therapeutics, antiparasitic treatments, biosensors, medical device coatings, and bioimaging.¹⁵³

Predominant causative agents of superficial fungal infections include Dermatophytes, *Malassezia*, and *Candida* species. AgNPs have demonstrated significant antifungal activity against the pathogens responsible for these superficial mycoses. It exhibited remarkable inhibitory effects against all tested clinical isolates of *Malassezia furfur in vitro*, with MIC values all below 0.5 mg/L.¹⁵⁴ Furthermore, no antagonism was observed when AgNPs were used in combination with ketoconazole (KTZ), with some combinations even showing synergistic effects. Notably, AgNPs possess the ability to accumulate and sustain the release of silver ions in skin lesion areas, particularly those rich in sebaceous glands, which helps prolong the antimicrobial efficacy. AgNPs also exhibit antifungal activity against Dermatophytes, such as *Trichophyton rubrum*, with MICs ranging from 0.25 to 2.5 µg/ml. This efficacy was superior to that of FLC.¹⁵⁵ In addition, Zhou et al. prepared a new iturin-AgNPs. The antifungal efficacy of these nanoparticles against *C. albicans* (MIC: 1.25-5 µg/mL) was stronger than that of traditional AgNPs and some antifungal drugs, with an extremely low risk of drug resistance and high biosafety. In animal experiments, the chitosan composite dressing made from it significantly promoted the healing of *C. albicans* infected wounds without causing organ damage.¹⁵⁶

Hassan et al. found that thioglycolic acid (TGA)-modified AgNPs significantly inhibited various *Aspergillus* species.¹⁵⁶ In experiments, wool fabric treated with TGA-AgNPs reduced the hyphal growth density of *A. brasiliensis*, demonstrating moderate antifungal activity. In contrast, they completely inhibited the growth of both hyphae and spores in *A. fumigatus*. Xia et al. reported that the MIC of AgNPs against the opportunistic pathogen *Trichosporon asahii* was 0.5-1 µg/mL, outperforming most common antifungal drugs (including AMB, 5-fluorocytosine, CAS, terbinafine, FLC, and ITR) and was only slightly less active than VRC. These AgNPs were found to inhibit *T. asahii* growth by penetrating fungal cells and disrupting various cellular components, including ribosomes, chromatin, mitochondria, cell membrane, and cell wall.¹⁵⁷

More importantly, this antifungal activity of AgNPs has been shown to be effective against multidrug-resistant fungi. Addressing drug-resistant *C. albicans*, Kamli et al. biosynthesized bimetallic Ag-Ni NPs using an aqueous leaf extract of *Salvia*.¹⁵⁸ These Ag-Ni bimetallic nanoparticles exhibited remarkable anti-*C. albicans* activity, particularly against FLC-resistant strains, with a MIC of 1.56 µg/mL. Furthermore, they assessed the impact of these NPs on biofilm formation, drug efflux pumps, and membrane integrity. The MFC (3.12µg/mL) and MIC (1.56µg/mL) values indicated strong antifungal properties of Ag-NiNPs against FLC-resistant *C. albicans*. Additionally, Ag-NiNPs blocked

the efflux pumps in FLC-resistant *C. albicans* and produced a strong synergistic effect when combined with FLC. Malik et al. reported that polyphenol-coated AgNPs (CC-AgNPs), prepared via green biosynthesis, exhibited good antimicrobial activity against *C. auris* by inducing S-phase/G2-M phase cell cycle arrest, mitochondrial damage, DNA fragmentation, and pro-apoptotic effects. At effective concentrations, they showed negligible hemolysis against red blood cells, indicating high safety and good biocompatibility.¹⁵⁹

Furthermore, AgNPs demonstrated excellent antimicrobial activity against several other severe pathogenic fungi. Zhang et al. synthesized a novel core-shell nanostructure composed of a palladium (Pd) core and a silver (Ag) shell, termed Pd@Ag Nanosheets (Pd@AgNSs). Results indicated that Pd@AgNSs inhibited various *Cryptococcus* species, with the *C. neoformans* complex being the most sensitive (MIC=0.25-2.0µg/mL). This activity was significantly superior to FLC and comparable to AMB. Notably, Pd@Ag NSs remained effective against FLC-resistant *Cryptococcus* strains. Transmission electron microscopy revealed that Pd@AgNSs treatment caused morphological aberrations, disorganized cell wall structure, separation of the cell membrane from the capsule, increased intracellular vacuoles, and reduced ribosomes in *cryptococcal* yeast cells.¹⁶⁰

Beyond their outstanding *in vitro* antifungal activity, AgNPs coated onto contact lenses have shown antifungal properties in an ocular infection model. AgNP-coated contact lenses exhibited a good therapeutic effect in a rabbit model of fungal keratitis induced by *A. fumigatus*.¹⁶¹ Three days post-infection, the eyes of rabbits in the control group became opaque, whereas those with AgNP-coated contact lenses remained clear. After 16 days, the control group eyes were uniformly opaque and exhibited severe hypopyon, while rabbits in the AgNPs-coated lens group still had discernible pupils. Hematoxylin and eosin staining of the eyes demonstrated significantly improved corneal pathology in the AgNPs-coated lens group compared to the control group.

3.2.2 Gold nanoparticles (AuNPs)

AuNPs have emerged as a prominent focus of research in recent years due to their excellent biocompatibility, low toxicity, and multifunctional properties. Typically ranging in size from 20 to 300 nm, AuNPs are increasingly synthesized via green synthesis methods. *In vitro* studies have demonstrated that AuNPs exhibited antifungal activity against a broad spectrum of fungal species, including *Microsporum gypseum*, *T. rubrum*, *C. albicans*, *Aspergillus* species and *F. oxysporum*.⁷⁹ The

antifungal efficacy of AuNPs is closely correlated with their size and morphology. A comparative study utilizing different reducing agents produced two distinct types of AuNPs: nanodiscs with an average diameter of 25 nm and polyhedral nanoparticles averaging 30 nm. Surface area analysis showed that the 25 nm nanodiscs exhibited a higher specific surface area (179.5 m²/g) compared to the polyhedral particles (150.5 m²/g). Correspondingly, the gold nanodiscs demonstrated superior fungicidal activity against *Candida* species. The MIC₈₀ values were 16–32 µg/mL for the 25 nm AuNPs and 32–128 µg/mL for the 30 nm AuNPs, suggesting that smaller particle size enhances antifungal potency. These findings align with conclusions reported in other studies.^{162,163}

Furthermore, AuNPs serve as a versatile platform for nanobiological assembly owing to their multiple surface functional groups and unique physicochemical characteristics. Gold nanoparticle-based bioconjugates have been successfully employed in the development of novel biomaterials for biological research. Milanezi et al. synthesized quercetin-coated gold nanoparticles (AuNPsQct), which displayed significant antifungal activity against *A. fumigatus*. The minimum inhibitory concentrations (MICs) against three clinical isolates (WT35, AF293, and CEA17) ranged from 0.1 to 0.38 mg/mL, underscoring their strong antifungal potential.¹⁶⁴ Rahimi et al. constructed a novel nanocomplex by covalently conjugating the host defense peptide indolicidin to AuNPs with an average particle size of approximately 30 nm. *In vitro* evaluations demonstrated that this nanocomplex exerted potent antifungal effects against FLC-resistant *C. albicans*. Moreover, the nanocomplex effectively downregulated the expression of the drug resistance-associated gene *ERG11*. Cytotoxicity assessments revealed no significant adverse effects on NIH3T3 fibroblasts or human red blood cells, indicating improved safety relative to both free peptides and FLC. Additionally, the complex significantly suppressed iNOS gene expression in macrophages, highlighting its immunomodulatory and anti-inflammatory capabilities.¹⁶⁵

3.2.3 Copper nanoparticles (CuNPs)

Cu is a non-toxic heavy metal and one of the essential trace elements for the human body, participating in numerous important metabolic processes within the human body. The particle size range of CuNPs is 2–350 nm, and most of them are prepared by the chemical reduction method.⁷⁹ CuNPs prepared by green synthetic methods show good environmental friendliness and biocompatibility.¹⁶⁶ In recent years, the application of CuNPs and their oxides (CuO NPs) in the field

of antifungal agents has received extensive attention. CuNPs of different morphologies and sizes (such as spherical, polygonal, marigold-petal-like and wirelike, with particle sizes ranging from 20 to 50 nm) all exhibited dose-dependent antifungal activity. CuNPs were reported to have antifungal activities against a various types of fungi, including *C. albicans*, *C. tropicalis*, *A. flavus*, *A. niger*, *F. equiseti*, *F. oxysporum*, *F. culmorum*, *A. alternate*, *Corticium salmonicolor*, *Curvularia lunata*.⁷⁹

The copper sulfide nanoparticles (pCuS NPs) coated with citrus pectin showed good antifungal and antibiofilm activities against *C. albicans*, which causes diabetic foot infection. Among them, the minimum inhibitory concentration (MIC) against *C. albicans* was 31.25 μ M, and the biofilm inhibitory concentration (BIC) was 15.63 μ M, which could effectively inhibit fungal adhesion and biofilm formation. Scanning electron microscopy and optical microscopy observations confirmed that the biofilm structure in the treatment group was significantly reduced. In addition, pCuS NPs significantly inhibited the transformation of yeast to mycelial morphology, reduced the secretion of extracellular polysaccharides (EPS) and the hydrophobicity of the cell surface (CSH), thereby interfering with the expression of key virulence factors.¹⁶⁷ In the face of the problem of multi-drug resistant fungi, CuNPs have also demonstrated certain therapeutic potential. A study prepared a novel nanocomposite material based on copper oxide nanoparticles (CuONPs) synthesized by fungi, nano-starch and nano-chitosan. The antifungal experiment showed that this nanocomposite material had a significant inhibitory effect on the multi-drug resistant *C. glabrata* MTMA 21 and *C. tropicalis* MTMA 24. The inhibitory zones were 27 mm and 28 mm respectively, and the minimum inhibitory concentration (MIC) was 125 μ g/mL for both. Cytotoxicity tests indicated that it was safe for Vero cells (IC_{50} = 312.8 μ g/mL). Transmission electron microscopy observations revealed that after treatment, the cell walls of *C. tropicalis* ruptured, the cell membranes disintegrated, and the contents of the cells leaked, ultimately leading to cell death.¹⁶⁸

3.2.4 Zinc oxide nanoparticles (ZnONPs)

ZnONPs is a metal oxide nanoparticle with a particle size of less than 100 nm and is the most widely studied metal oxide NPs in antifungal applications. One of the reasons for its prominent position in the literature is that the commonly used fungicides in agriculture are mainly composed of zinc compounds.⁷⁹ Recent advances in nanomaterial engineering have employed various strategies, including elemental doping, surface modification and size control, to enhance the properties of zinc

oxide (ZnO). This has led to the development of diverse ZnO nanomaterials—such as pure nano-ZnO, 5% Pd-doped nano-ZnO, chitosan-linoleic acid-coated ZnO NPs, and ZnO quantum dots.¹⁵³ It has been found that those ZnONPs have antifungal activities against a variety of fungi, including *T. mentagrophytes*, *M. canis*, *C. albicans*, *Aspergillus* spp., *Fusarium* spp., *A. alternata*, *A. solani*, etc.¹⁴⁵ Firstly, ZnONPs have shown great potential or prospects in the prevention and treatment of superficial fungal infections in humans. Fungal foot infection is a common superficial fungal infection and is recognized as an important public health problem. A study evaluated the ability of socks coated with ZnONPs to inhibit fungal growth in an *in vitro* model mimicking real-life situations. The results showed that after co-incubation of foot skin scales infected by fungi with socks coated with zinc oxide nanoparticles for 24 hours, the positive rate of fungal culture was only 54.8%, while the positive rate of the control group that was not incubated was 100%.¹⁶⁹ A study reported the green synthesis of zinc oxide nanoparticles (ZnONPs) using the petal extract of *Rosa indica* L. and evaluated their antifungal efficacy against *T. mentagrophytes* and *M. canis*. Both the synthesized ZnONPs and a formulated nanopaint containing ZnONPs exhibited significant *in vitro* antifungal activity against the tested dermatophytes. Furthermore, the antifungal effect was enhanced when ZnONPs were combined with ketoconazole, suggesting a synergistic interaction.¹⁷⁰ A novel synthetic xerogel incorporating AgNPs and ZnONPs was developed and evaluated for its antidermatophytic activity. The xerogel showed significant antifungal activity in a concentration-dependent manner, with *T. mentagrophytes* exhibiting higher susceptibility compared to *T. verrucosum*. The enhanced antifungal effect of the AgZnO xerogel, particularly at lower concentrations, suggested synergistic interactions between the two metal nanoparticles.¹⁷¹

ZnONPs also have a synergistic effect with antifungal drugs. Poojary et al. successfully prepared a ketoconazole-coated zinc oxide nanoparticle (KTZ-coated ZnONPs) by green synthesis method. It showed that KTZ-coated ZnONPs had a significantly better inhibitory effect on *M. furfur* than free KTZ. Although ZnO-GTE nanoparticles themselves did not exhibit anti-*Malassezia* activity, they effectively enhanced the antifungal efficacy of KTZ as carriers.¹⁷²

In addition, ZnONPs also exhibited a significant inhibitory effect on drug-resistant *Candida* and other molds. Spherical ZnO-np (particle size 20-40 nm) synthesized by sol-gel method showed significant antifungal activity against *C. albicans* derived from urinary tract infections. At sub-inhibitory concentrations (Sub-MIC), ZnO-np significantly inhibited the initial adhesion ability of

C. albicans and down-regulated the expression of *ALS1* and *ALS3* genes, especially in FLC-resistant strains, the effect was more obvious.¹⁷³ Khan et al investigated the antifungal potential of green-synthesized zinc oxide nanoparticles (ZnONPs) using *Monothea buxifolia* leaf extract. The biosynthesized ZnONPs, characterized as spherical with an average size of 45.8 nm, exhibited antifungal activities against *F. solani*, *A. fumigatus*, *A. niger*, *A. flavus* and *Mucor* species.¹⁷⁴

3.2.5 Titanium dioxide nanoparticles (TiO₂NPs)

TiO₂NPs, as a safe, stable and photocatalytic inorganic nanomaterial, showed broad application prospects in controlling fungal infections, especially in the fields of environmental disinfection and medical material protection. TiO₂NPs had significant inhibitory effects on a variety of pathogenic fungi, especially showing good antifungal effects on *Candida* spp. and *Aspergillus* spp.⁷⁹ Under light conditions, TiO₂NPs co-doped with N and F can effectively inactivate oral *C. albicans* by generating ROS.⁷⁹ A study explored the potential antifungal effect of green synthesized TiO₂ nanogel (GSTG) from *Caralluma fimbriata* against *C. albicans* infection in African catfish (*Clarias gariepinus*). The results showed that water exposure to 2.00 mg/L of green synthetic TiO₂ nanogel (GSTG) could effectively alleviate various physiological and pathological disorders of African catfish caused by *C. albicans* infection.¹⁷⁵ Zacarías et al. developed a carbon-doped TiO₂ photocatalytic paint, which demonstrated potent, irreversible inactivation of *A. niger* conidia under UV light, achieving 1.4-fold higher efficacy than controls. Microscopy revealed severe structural damage to the conidia, and the paint also significantly suppressed mycelial growth, indicating its broad antifungal potential.¹⁶⁶ In addition, a research has revealed that a chitosan coating with 0.5% nano-TiO₂ showed enhanced antifungal activity against mango rot fungi, achieving 100% inhibition of *Cladosporium oxysporum* and *Colletotrichum gloeosporioides*, and significantly increasing the mortality of *P. steckii* to 75.4% via membrane disruption.¹⁷⁶

3.2.6 Iron oxide nanoparticles (IONPs)

IONPs are a type of metal oxide with biodegradability, low cytotoxicity, magnetism, and an active surface that can be altered by biocompatible coatings. It has been used in medical diagnostic imaging, targeted drug delivery, and various other biomanufacturing and therapeutic applications.⁷⁹ Recent studies have found that IONPs, including maghemite (γ -Fe₂O₃) and magnetite (Fe₃O₄)NPs, also possessed

functions such as broad-spectrum, high efficiency, and low toxicity, and show great potential in dealing with drug-resistant fungi and complex deep fungal infections.¹⁶⁶ Fe₂O₃NPs with a diameter of 10–30 nm exhibit inhibitory effects against filamentous fungi such as *A. alternata* and *A. niger*. Fe₃O₄NPs showed antifungal activity against *Candida* species. Notably, Fe₃O₄NPs effectively inhibited *C. albicans* biofilm formation. Functionalized Fe₃O₄ nanoparticles could enhance sensitivity and reduce biofilm mass in FLC-resistant strains.¹⁷⁷

Meantime, Lopes et al. demonstrated a dose-dependent effect of bionized nanoferrite IONPs (BNF-IONPs) in a murine cryptococcal pneumonia model. Notably, low-dose BNF-IONPs significantly reduced fungal burden and improved survival by modulating the host immune response, specifically by lowering pro-inflammatory cytokines (IL-2, IL-4, TNF- α), rather than through direct fungicidal activity.¹⁷⁸ Anghel et al. developed a wound dressing coated with functionalized IONPs (magnetite, Fe₃O₄) and Satureja hortensis essential oil. This hybrid nanosystem effectively inhibited *C. albicans* adhesion and biofilm formation, and demonstrated stable loading of the volatile oil.¹⁷⁹ IONPs inhibited drug-resistant *Candida* spp growth and could alter the gene expression of these microorganisms. Zare-Khafr et al. synthesized a new magnetic IONPs, which exerted antifungal activity against fluconazole-resistant *C. albicans* and downregulated the expression of the *ERG11* gene. This led to a significant reduction in cellular ergosterol content, confirming a novel mechanism of action that circumvents existing resistance mechanisms.¹⁸⁰

3.2.7 Other antifungal metal nanoparticles

A variety of other types of metallic nanoparticles (MNPs) have been explored as potential antifungal agents. For instance, nanoparticles made from aluminum oxide (Al₂O₃NPs), magnesium oxide (MgONPs), bismuth trioxide (Bi₂O₃NPs), and noble metals such as platinum and palladium (similar to gold and silver) showed antifungal activities to varying degrees. Al₂O₃NPs and MgONPs exhibited potential antifungal activity against *F. oxysporum*.^{181,182} Zirconia (ZrO)NPs demonstrated growth inhibition effects against *C. albicans* and *A. niger*.¹⁸³ Unfortunately, only qualitative studies on the antifungal properties of these particles have been conducted so far, without quantitative results. The antifungal effectiveness of these particles remains unclear, and their antifungal mechanisms are yet to be investigated.

Platinum (Pt) nanoparticles with sizes of 10–50 nm showed efficient antifungal activity against *Colletotrichum acutatum* and *Cladosporium fulvum*.¹⁸⁴ Palladium (Pd) nanoparticles with mean sizes ranging from 200 nm to 550 nm exhibited significant growth inhibition against *Colletotrichum gloeosporioides* and *F. oxysporum*.¹⁸⁵ The size of Pd NPs played a critical role in their antifungal activity, with the smallest particles showing the highest efficacy. Bi₂O₃NPs displayed antifungal activity against *C. albicans* and showed complete suppression of biofilm formation.¹⁸⁶ However, many of the above-mentioned studies failed to quantify the antifungal activity of these nanoparticles or investigate their antifungal mechanisms, and their cytotoxicity toward mammalian cells has not yet been evaluated.

3.2.8 Antifungal mechanisms and applicable scenarios of metal nanoparticles

Metal nanoparticles exhibit antifungal activity through multiple distinct mechanisms (Figure 2), such as disrupting the fungal cell wall and membrane, releasing bioactive metal ions, inducing excessive ROS production, depleting intracellular ATP levels, and damaging essential cellular components, including mitochondria, proteins, and DNA.⁷⁰ The surfaces of these metal nanoparticles are typically positively charged, enabling electrostatic interactions with the negatively charged components of fungal cell walls, thereby facilitating adhesion to the fungal cell surface. Upon exposure, metal nanoparticles can induce significant structural alterations in fungal cell walls, including surface contraction, cellular aggregation, pit and pore formation, and overall morphological deformation. Concurrently, these nanoparticles may bind to sulfhydryl (-SH) and phosphate groups present on cell walls and membranes, leading to changes in membrane permeability. This ultimately compromises the structural integrity of both the cell wall and cytoplasmic membrane.¹⁶⁶ Once internalized, metal nanoparticles can release metal ions that promote the generation of ROS (e.g., hydroxyl radicals and singlet oxygen), interfere with protein function, disrupt mitochondrial calcium homeostasis, impair the electron transport chain, inhibit respiratory activity, and lead to mitochondrial dysfunction. Additionally, these ions may damage critical cellular components, including ribosomes and DNA, thereby disrupting energy metabolism and replication processes and ultimately triggering cell death. Furthermore, certain metal nanoparticles have been shown to inhibit fungal biofilm formation.¹⁶⁶ In addition, metal nanoparticles can enhance and prolong their fungicidal efficacy through physical and mechanical damage mechanisms.¹⁸⁷

These nanoparticles are used in different scenarios, and different nanoparticles have distinct applicable scenarios. AgNPs are suitable for superficial skin/mucosal infections, medical device coatings and multidrug-resistant fungi. AuNPs are preferred when high biocompatibility and low toxicity are required and as a platform for bioconjugation with antifungal peptides. CuNPs are effective against diabetic foot infections and multidrug-resistant *Candida* species, with strong antibiofilm activity. ZnONPs are widely used in agriculture and superficial infections and in synergistic combination with conventional drugs. TiO₂NPs are suitable for environmental disinfection and material protection under light conditions. IONPs appropriate for deep or systemic infections (e.g., cryptococcosis) due to biodegradability, magnetism, and immunomodulatory effects.

4. Conclusion and Prospect

The global surge in invasive fungal infections, compounded by the relentless emergence of multidrug-resistant pathogens—most notably *Candida auris*—has laid bare the profound limitations of conventional antifungal therapeutics, which struggle with suboptimal efficacy, dose-limiting host toxicity, and rampant resistance development. In this unmet clinical landscape, drug repurposing and nanomaterial-based antifungal strategies have emerged as promising avenues to address these unmet medical needs.

Mounting preclinical evidence confirms that a diverse array of non-antifungal medications (antibacterial drugs, antiparasitic drugs, antiviral drugs and etc) possess either intrinsic fungicidal/fungistatic activity or striking synergistic potential when combined with mainstream antifungals. Standalone candidates including clioquinol, miltefosine, auranofin, and sertraline display broad-spectrum potency against MDR fungi, while combinatorial pairings frequently restore susceptibility to first-line agents that have been rendered ineffective by resistance. Concurrently, nanotechnology-driven innovations—spanning polymeric nanoparticles and metal-based nanosystems—deliver multifaceted advantages: they drastically improve drug solubility and bioavailability, enable targeted delivery to infection foci and biofilms, reduce off-target organ toxicity, and exert intrinsic antifungal effects via multi-modal mechanisms that impede resistance evolution.

Despite these transformative advances, the translational gap between bench and bedside remains substantial. Most investigations remain confined to *in vitro* and early *in vivo* preclinical models, with scarce clinical validation and limited understanding of *in vivo* pharmacokinetic–pharmacodynamic

(PK–PD) relationships.

Future efforts should focus on clarifying the molecular targets, signaling pathways, and synergistic mechanisms of repurposed drugs and nanomaterials, characterizing structure–activity relationships and biosafety of nanosystems, rationally optimizing combination regimens with low toxicity and high resistance barriers via standardized models and stimuli-responsive delivery systems, and accelerating clinical translation through phased clinical trials, biomarker development, and regulatory and safety evaluations to translate these innovative strategies into safe and effective antifungal therapies.

In sum, the integration of drug repurposing and advanced nanotherapeutics offers a viable, accelerated pathway to counter the global fungal threat. By prioritizing mechanistic clarity, rational combination design, and expeditious clinical translation, these interdisciplinary approaches will yield safer, more effective, and resistance-refractory antifungal therapies, ultimately reducing the profound morbidity and mortality attributable to fungal diseases worldwide.

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Conflicts of interest

There are no conflicts of interest.

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