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REVIEW

# Next-generation antifungal drugs: Mechanisms, efficacy, and clinical prospects

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Clinical efficacy;
Combination therapy strategies

**Abstract** Invasive fungal infections (IFIs) have become prominent global health threats, escalating the burden on public health systems. The increasing occurrence of invasive fungal infections is due primarily to the extensive application of chemotherapy, immunosuppressive therapies, and broad-spectrum antifungal agents. At present, therapeutic practices utilize multiple categories of antifungal agents, such as azoles, polyenes, echinocandins, and pyrimidine analogs. Nevertheless, the clinical effectiveness of these treatments is progressively weakened by the emergence of drug resistance, thereby substantially restricting their therapeutic utility. Consequently, there is an imperative need to expedite the discovery of novel antifungal agents. This review seeks to present an exhaustive synthesis of novel antifungal drugs and candidate agents that are either under current clinical investigation or anticipated to progress into clinical evaluation. These emerging compounds exhibit unique benefits concerning their modes of action, antimicrobial spectra, and pharmacokinetic characteristics, potentially leading to improved therapeutic outcomes relative to conventional antifungal regimens. It is anticipated that these novel therapeutic agents will furnish innovative treatment modalities and enhance clinical outcomes in managing invasive fungal infections.

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## 1. Introduction

Invasive fungal infections (IFIs), chiefly attributable to species of *Candida*, *Aspergillus*, and *Cryptococcus*, exhibit substantially higher mortality rates than superficial fungal infections, which are more frequently encountered. These infections have become increasingly urgent global health issues; the World Health Organization has reported a marked rise in incidence, particularly among immunocompromised individuals, patients in intensive care, and those with respiratory disorders during the ongoing pandemic[1]. Epidemiological analyses indicate that annual fatalities from fungal infections surpass those caused by malaria and breast cancer, with mortality rates rivaling those reported for tuberculosis and Acquired Immune Deficiency Syndrome (AIDS)[1]. Furthermore, the prevalence of opportunistic fungal infections is a rising trend associated with the expanded use of chemotherapy, immunosuppressive therapies, and broad-spectrum antibiotics[2,3].

In clinical practice, most antifungal therapies are designed to disrupt key structural components of fungal cells, notably the cell wall and cell membrane[4-6]. These agents include echinocandins, which inhibit $\beta$-glucan synthesis in the cell wall; azoles and allylamines, which impair ergosterol biosynthesis; and polyenes, which bind ergosterol to compromise membrane integrity[7-9] (Table 1). Additionally, antifungal drugs targeting intracellular proteins hinder fungal proliferation by inhibiting nucleic acid synthesis, disrupting the electron transport chain, or impairing microtubule dynamics[10,11] (Fig. 1, Table 2[12-34]). Nevertheless, the clinical utility of these therapies is increasingly challenged by the emergence of drug-resistant fungal strains.

The emergence of fungal resistance is a multifactorial process driven by genetic alterations, adaptive evolution, and both environmental and clinical influences[35-37]. Key resistance mechanisms include mutations at drug target sites, increased efflux of antifungal agents, metabolic reprogramming, and biofilm formation[38]. For example, mutations in the CYP51 enzyme encoded by the *ERG11* gene substantially reduce the binding affinity of azole drugs, thereby impairing their efficacy[39,40]. Similarly, alterations in the *FKS* gene, which encodes the catalytic subunit of $\beta$-1,3-glucan synthase, result in diminished sensitivity to echinocandins[41-43]. Additionally, fungi may increase the expression of ATP-binding cassette (ABC) or major facilitator superfamily (MFS) transporters, promoting drug efflux, lowering intracellular concentrations, increasing drug efflux, and reducing intracellular drug concentrations, further conferring resistance[44-46]. Metabolic reprogramming further contributes to resistance, as fungal cells modify the ergosterol composition or activate alternative pathways to bypass drug inhibition[47]. Moreover, biofilm formation creates a physical barrier that restricts antifungal penetration, thereby exacerbating resistance[48,49]. Clinical and environmental factors also play significant roles; prolonged or inappropriate antifungal use selects for resistant strains, and cross-resistance further complicates treatment[39,40]. The spread of resistant strains in hospital settings, compounded by host immunosuppression, ultimately intensifies the challenge of managing fungal infections.

Strategies to combat fungal drug resistance in clinical settings encompass several approaches. First, the development of novel antifungal agents increasingly relies on high-throughput screening and computational chemistry to design and optimize compounds with innovative molecular architectures, thereby circumventing established resistance mechanisms and enhancing therapeutic efficacy[50-54]. Second, research on natural products has gained prominence, with considerable efforts focused on isolating compounds with unique antifungal properties from plants, microorganisms, and other natural sources[55,56]. These bioactive natural substances not only exert direct antifungal effects but also work synergistically with existing therapies, thereby improving efficacy and mitigating the risk of resistance. Additionally, drug repurposing strategies-which involve reexamining the potential antifungal applications of already approved medications by leveraging their well-characterized safety and pharmacokinetic profiles-facilitate rapid clinical translation and broaden treatment options[57-59]. Immunotherapeutic approaches are also advancing, as investigations into monoclonal antibodies, vaccines, and other immunomodulatory modalities aim to augment host immune responses and improve resistance to fungal infections (Fig. 2)[60-62]. Finally, breakthroughs in genomics and proteomics have enabled the identification of novel therapeutic targets, such as enzymes involved in cell wall biosynthesis, key signaling pathways, and stress response mechanisms, thereby paving the way for precision antifungal interventions[63-65]. Collectively, these complementary strategies foster the development of personalized antifungal treatment systems, ultimately leading to improved patient outcomes and reduced healthcare costs.

Recent advances in medicine have paved the way for innovative antifungal agents that exhibit robust clinical efficacy in managing invasive fungal infections. This review examines emerging antifungal drugs—many currently in clinical trials or expected to enter clinical evaluation soon—along with promising compounds that may offer novel therapeutic alternatives in the future. These agents are engineered either to target pathways not addressed by conventional therapies or to increase the effectiveness of established targets *via* innovative mechanisms. In contrast to traditional treatments, the compounds discussed herein confer distinct pharmacological advantages, including unique mechanisms of action, expanded antimicrobial spectra, and improved pharmacokinetic profiles, among other beneficial properties (Fig. 1). Collectively, these advancements have the potential to transform treatment strategies, offering promising prospects for preventing and controlling invasive fungal infections.

## 2. Traditional antifungal drugs

Conventional antifungal agents are indispensable in the management of fungal infections and primarily consist of polyenes, azoles, allylamines, and pyrimidine analogs[55,66]. These agents impede fungal proliferation *via* diverse mechanisms and are extensively utilized to address both superficial and invasive mycoses (Table 1).

**Table 1** Summary of the mechanisms of action and clinical application of traditional antifungals.

| Drug class | Representative drug | Mechanism of action | Target gene (Enzyme) | Clinical application | Common adverse effect | Resistance mechanism |
|---|---|---|---|---|---|---|
| Polyenes | Amphotericin B (liposomal) | Binds to ergosterol, forming membrane pores | ERG6 (sterol synthase) | Systemic fungal infections (*e.g.*, cryptococcal meningitis) | Nephrotoxicity, infusion-related reactions | Rare; toxicity limits use |
| | Nystatin | Binds to ergosterol, disrupting membrane integrity | ERG6 (sterol synthase) | Topical fungal infections (*e.g.*, oral candidiasis) | Local irritation, allergic reactions | Rare |
| Azoles | Fluconazole | Inhibits 14$\alpha$-demethylase, blocking ergosterol synthesis | ERG11/ CYP51 (14$\alpha$-demethylase) | Candidiasis, cryptococcosis | Hepatotoxicity, drug interactions | ERG11 mutations, efflux pump overexpression |
| | Itraconazole | Inhibits 14$\alpha$-demethylase, blocking ergosterol synthesis | ERG11/ CYP51 (14$\alpha$-demethylase) | Aspergillosis, histoplasmosis | Gastrointestinal discomfort, hepatotoxicity | ERG11 mutations, efflux pump overexpression |
| Echinocandins | Caspofungin | Inhibits $\beta$-(1,3)-D-glucan synthase, disrupting cell wall | FKS1/FKS2 (glucan synthase subunit) | Invasive candidiasis, aspergillosis | Elevated liver enzymes, infusion-related reactions | FKS mutations leading to reduced target affinity |
| | Micafungin | Inhibits $\beta$-(1,3)-D-glucan synthase, disrupting cell wall | FKS1/FKS2 (glucan synthase subunit) | Invasive candidiasis, empirical therapy in neutropenic patients | Elevated liver enzymes, infusion-related reactions | FKS mutations leading to reduced target affinity |
| Flucytosine | 5-Fluorocytosine (5-FC) | Converted to 5-fluorouracil, interfering with RNA and DNA synthesis | FCY2 (transporter), FUR1 (metabolic enzyme) | Cryptococcal meningitis (often combined with amphotericin B) | Bone marrow suppression, gastrointestinal discomfort | FCY2 transporter deficiency, FUR1 gene mutations |
| Allylamines | Terbinafine | Inhibits squalene epoxidase, blocking ergosterol synthesis | ERG1 (squalene epoxidase) | Dermatophytosis, onychomycosis | Hepatotoxicity, gastrointestinal discomfort | Rare |

This table summarizes the representative drugs, targets, main mechanisms of action, clinical indications and common adverse reactions of traditional antifungal drugs (including polyenes, azoles, echinocandins, flucytosine and acrylamide), and briefly lists the common resistance mechanisms.

Polyenes exhibit antifungal activity by interacting with ergosterol within the fungal cell membrane, thereby compromising membrane integrity and inducing the efflux of cytoplasmic constituents[67]. Among polyene antifungal agents, amphotericin B and nystatin serve as prototypical examples; notably, griseofulvin, while a conventional antifungal, belongs to a distinct class. Amphotericin B continues to be the primary therapeutic option for severe infections, including cryptococcal meningitis and invasive aspergillosis, although its marked nephrotoxicity substantially restricts its clinical use[68]. Nystatin is chiefly employed for the treatment of mucosal Candida infections, including oral and vaginal candidiasis, and is favored for topical administration owing to its minimal systemic toxicity[69].

Azoles function by inhibiting 14-$\alpha$-demethylase, thereby disrupting ergosterol biosynthesis and compromising fungal cell membrane stability[67]. Azoles are classified into first- and second-generation agents on the basis of their chronological development[70]. First-generation azoles, such as ketoconazole, are now primarily used topically due to their significant hepatotoxicity[71]. Second-generation agents, including fluconazole and itraconazole, are widely used in clinical practice. Fluconazole is commonly prescribed for *Candida* infections and cryptococcal meningitis, but has limited efficacy against *Candida glabrata* and *Candida krusei* and is associated with a risk of hepatotoxicity[70]. Itraconazole is effective in treating dermatophytosis and certain invasive fungal infections; however, its oral bioavailability is highly variable and influenced by individual patient factors and food intake[72].

Allylamines, which include terbinafine and naftifine, inhibit squalene epoxidase essential enzyme in ergosterol biosynthesis-thereby compromising fungal cell membrane integrity and culminating in fungal cell death[67]. These agents are predominantly indicated for the treatment of dermatophyte infections, including tinea manus, tinea pedis, and onychomycosis[67,73]. Nonetheless, given the risk of hepatotoxicity, vigilant monitoring of hepatic function is recommended during therapy.

Pyrimidine analogs, such as flucytosine, exert antifungal effects by disrupting RNA and DNA synthesis, thereby inhibiting fungal proliferation[67]. Clinically, flucytosine is frequently coadministered with amphotericin B for the treatment of cryptococcal meningitis; this combination improves therapeutic outcomes and diminishes the risk of resistance development[8]. Nevertheless, prolonged exposure to flucytosine may lead to bone marrow suppression, necessitating careful monitoring of hematologic parameters[74].

Although conventional antifungal agents remain clinically valuable, each drug class presents inherent limitations, including toxicity, resistance development, and pharmacokinetic challenges. In the context of increasing numbers of drug-resistant fungal strains and increasing clinical demands, the deficiencies of traditional therapies have become increasingly evident. Optimizing current treatment regimens through combination therapy and

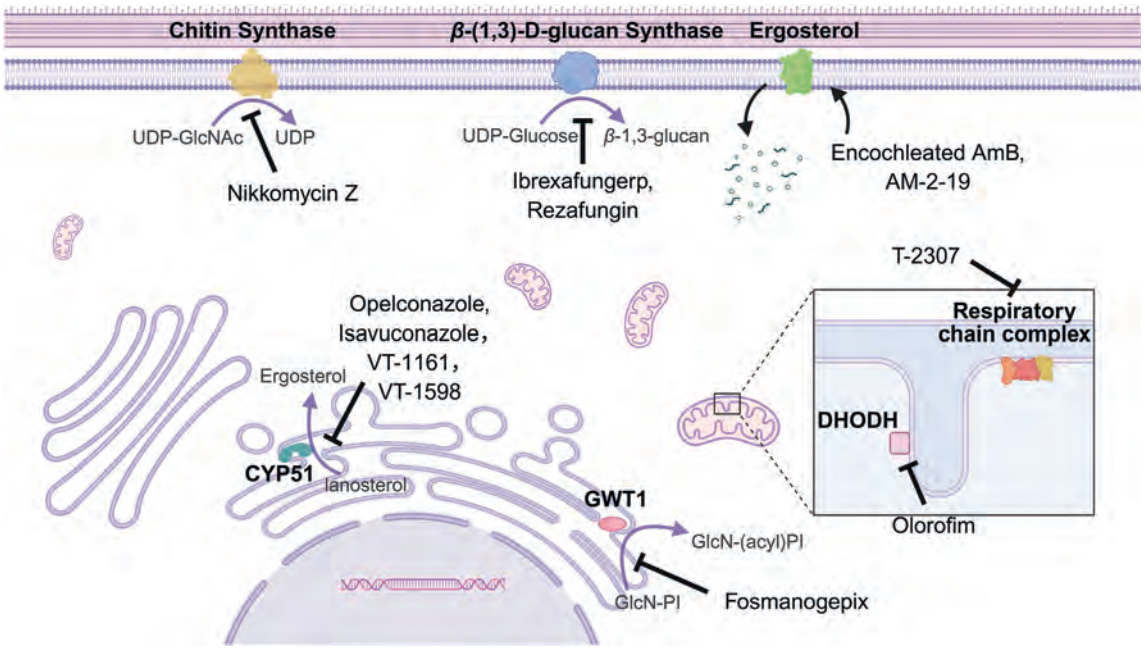


**Figure 1** Schematic representation of the mechanism of action of novel antifungal agents currently in clinical trials. Ibrexafungerp and rezafungin predominantly inhibit β-(1,3)-D-glucan synthase, thereby preventing glucan synthesis. Nikkomycin Z disrupts chitin biosynthesis by competitively binding to UDP-GlcNAc binding sites. Fosmanogepix exerts its activity by partially inhibiting the Gwt1 enzyme, which interferes with GPI-anchored protein biosynthesis. Opelconazole, isavuconazole, VT-1598, and oteseconazole specifically target fungal CYP51, thereby impairing ergosterol synthesis. MAT2203 and AM2-19 directly bind to ergosterol in the fungal cell membrane, leading to membrane destabilization. Olorofim primarily targets fungal dihydroorotate dehydrogenase, thus disrupting nucleic acid production and inhibiting mycelial elongation. T-2307 exerts a selective inhibitory effect on the respiratory chain complex within yeast mitochondria, resulting in a decline in mitochondrial membrane potential. (Figure created with BioRender.com).

precise dose adjustments is essential for enhancing antifungal efficacy. Moreover, the development of safer and more potent agents, particularly next-generation triazoles and echinocandins, is critical for overcoming antifungal resistance. With multidisciplinary collaboration and the integration of advanced technologies, significant progress in the management of fungal infections is anticipated, offering more tailored therapeutic options and improved patient outcomes.

**Table 2** Activity of new antifungal agents currently in clinical trials against common pathogenic fungi.

| Pathogens&novel antifungals | *Candida* spp. | *Aspergillus* spp. | *Cryptococcus* spp. | *Mucor* spp. | *Fusarium* spp. | *Histoplasma capsulatum* | Ref. |
|---|---|---|---|---|---|---|---|
| Ibrexafungerp (SCY-078) | √ | √ | × | × | × | √ | 12,13 |
| Rezafungin | √ | √ | × | × | ? | ? | 13,14 |
| Nikkomycin Z | √ | √ | × | √ | × | √ | 15−17 |
| Fosmanogepix (APX001) | √ | √ | √ | √ | √ | ? | 18−21 |
| Opelconazole (PC945) | √ | √ | √ | ? | × | ? | 19,22−24 |
| Isavuconazole | √ | √ | √ | √ | × | √ | 25−27 |
| MAT2203 | √ | √ | √ | √ | ? | ? | 28 |
| AM-2-19 | √ | √ | × | | × | × | 29 |
| VT-1598 | √ | √ | √ | ? | ? | ? | 30 |
| Oteseconazole (VIVJOA®, VT-1161) | √ | × | √ | √ | × | √ | 13,31 |
| Olorofim | × | √ | × | × | √ | √ | 13,32 |
| T-2307 | √ | √ | √ | × | × | ? | 33 |
| VL-2397 | √ | √ | √ | ? | √ | ? | 34 |
| Legend | Potent activity (√) | | | No activity (×) | | Unkown (?) | |

√ Represents a study that reported significant activity of the drug against the corresponding fungi.
× Represents the study reporting that the drug had no significant activity against the corresponding fungi.
? Represents that no studies have reported the activity of the drug against the corresponding true bacteria.

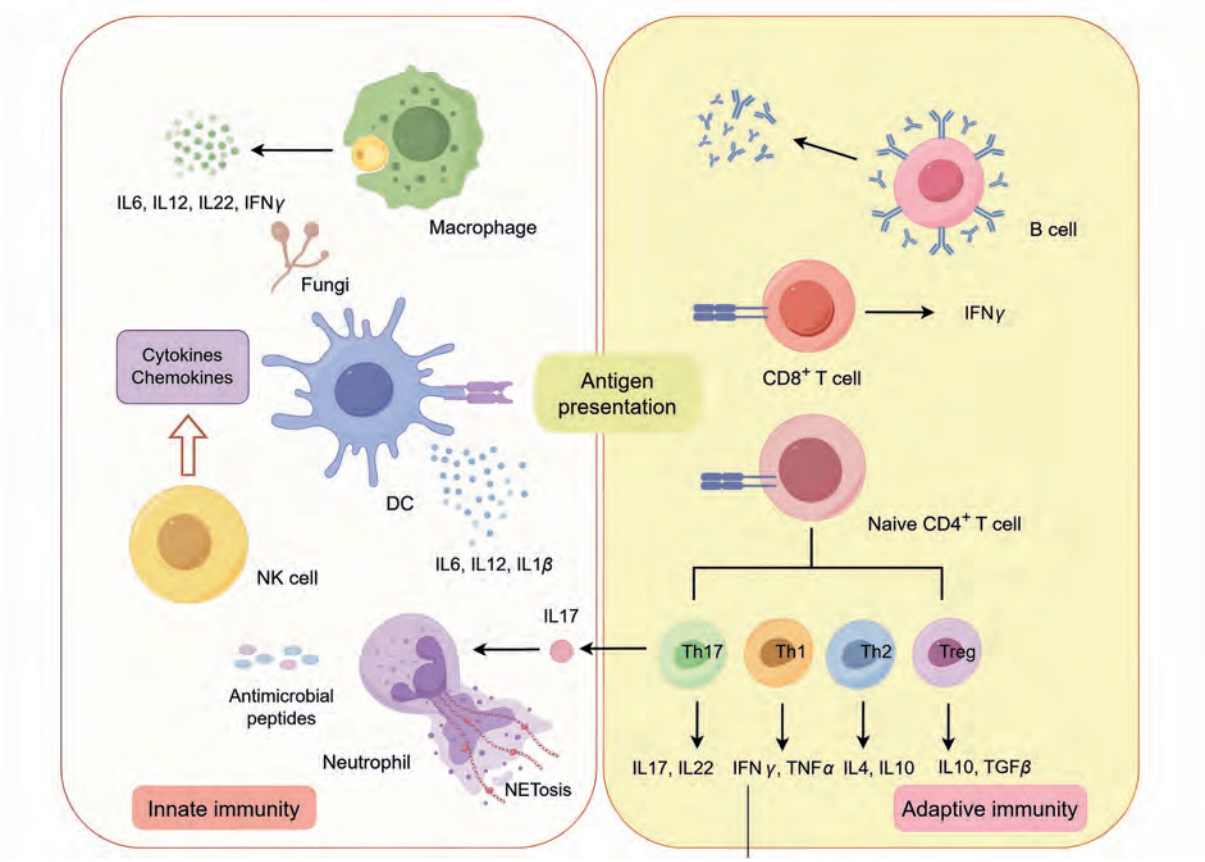


**Figure 2** The antifungal immune response is mediated through the coordinated interplay between innate and adaptive immunity. Upon fungal invasion, pattern recognition receptors (PRRs) recognize fungal cell wall components such as $\beta$-glucan, thereby initiating the phagocytic activity of effector cells, including macrophages and neutrophils, and promoting the release of pro-inflammatory cytokines, such as interleukin-1$\beta$ (IL-1$\beta$) and tumor necrosis factor-$\alpha$ (TNF-$\alpha$). Subsequently, dendritic cells activate adaptive immunity by presenting fungal antigens to $CD4^+$ T cells *via* major histocompatibility complex class II (MHC-II) molecules. This process drives the differentiation of Th1 cells, which secrete interferon-$\gamma$ (IFN-$\gamma$) to enhance macrophage-mediated pathogen killing, and the activation of Th17 cells, which promote neutrophil recruitment through interleukin-17 (IL-17). B cells generate pathogen-specific antibodies, such as immunoglobulin G (IgG), facilitating opsonization and enhancing phagocytosis for effective pathogen clearance.

## 3. Novel drugs and compounds that directly target fungi

### *3.1. Antifungals targeting the cell wall*

The fungal cell wall comprises primarily $\beta$-1,3-glucan, $\beta$-1,6-glucan, chitin, and various proteins, all of which are essential for its structural integrity and mechanical resilience. These components interact to form an intricate network that underpins the overall functionality of the fungal cell[75]. The cell wall plays dual roles: it acts as a protective barrier against environmental stressors and is critical to fundamental cellular processes such as maintaining cell morphology, facilitating nutrient and ion transport, and modulating signal transduction pathways. Consequently, antifungal therapies that target the synthesis or functionality of these vital cell wall constituents can effectively inhibit fungal growth and reproduction (Table 3)[76].

#### *3.1.1. Inhibitors of glucan synthase*

Glucan synthase, the enzyme that catalyzes $\beta$-(1,3)-D-glucan production, is a membrane-associated protein localized at the plasma membrane that harbors conserved catalytic domains known as FKS. The RHO1 GTPase subunit modulates its activity[77]. Inhibitors of $\beta$-(1,3)-D-glucan synthase constitute a class of compounds that exert antifungal effects by interfering with the biosynthesis of $\beta$-(1,3)-D-glucan[76]. Given that $\beta$-(1,3)-D-glucan is not present in mammalian cells, these inhibitors display remarkable specificity and negligible toxicity. As an essential enzyme for fungal cell wall biosynthesis, glucan synthase is pivotal in preserving cellular architecture and integrity. Mutations in the FKS1 and FKS2 genes result in impaired cellular growth, and simultaneous deletion of these genes precipitates cell death, thereby underscoring glucan synthase as an appealing pharmacological target[78]. Echinocandin resistance, a significant challenge in antifungal therapy, predominantly originates from genetic mutations affecting $\beta$-(1,3)-D-glucan synthesis, especially those affecting the glucan synthase enzyme[77]. Current efforts in developing glucan synthase inhibitors focus on obstructing the elongation of the glucan polymer by binding to Fks1p, thereby preventing the accumulation of $\beta$-(1,3)-D-glucan within the fungal cell wall and promoting potent antifungal activity.

*3.1.1.1. Ibrexafungerp (SCY-078).* Ibrexafungerp belongs to a class of drugs known as triterpenoid antifungal agents (Fig. 3). These agents impede the process of synthesizing fungal cell walls

**Table 3** Mechanisms of action of new antifungal drugs currently in clinical trials and the latest clinical trial results.

| Novel antifungal agent | | Route of administration | Half-life | Target molecule | Latest clinical progress | ClinicalTrials.gov ID |
|---|---|---|---|---|---|---|
| Antifungals targeting cell wall | Ibrexafungerp (SCY-078) | Oral (intravenous formulation under development) | 20−25 h | 1,3-β-D-Glucan synthase | Phase III completed for vulvovaginal candidiasis | NCT05399641 |
| | | | | | Phase III completed for multiple drug-resistant fungi | NCT03059992 |
| | Rezafungin | Intravenous | 130 h | 1,3-β-D-Glucan synthase | Phase III for invasive candidiasis | NCT03667690 |
| | | | | | Phase II for pneumocystis pneumonia (PCP) | NCT05835479 |
| | Nikkomycin Z | Oral | 1−2 h | Chitin synthase | Phase II for coccidioidomycosis | NCT00614666 |
| | Fosmanogepix | Oral and intravenous | 20−26 h (IV) 35 h (*PO*) | Gwt1 protein | Phase III for candidiasis | NCT04148287 |
| | | | | | Phase II for invasive fungal infections | NCT04240886 |
| Antifungals targeting cell membranes | Opelconazole | Nebulisation | 138 h | CYP51A1 | Phase III for invasive pulmonary aspergillosis | NCT05238116 |
| | Isavuconazole | Oral and intravenous | 130 h | CYP51 (lanosterol 14α-demethylase) | Phase IV for invasive fungal disease (IFD) | NCT05630976 |
| | Encochleated amphotericin B (MAT2203) | Oral | − | Ergosterol | Phase III for cryptococcal meningitis | NCT05541107 |
| | | | | | Phase II for vulvovaginitis | NCT02971007 |
| | VT-1598 | Oral | 80−100 h | CYP51 (lanosterol 14α-demethylase) | Phase I for coccidioidomycosis | NCT04208321 |
| | Oteseconazole (VT-1161, VIVJOA®) | Oral | 138 h | CYP51 (lanosterol 14α-demethylase) | Phase III for vulvovaginal candidiasis | NCT03562156 |
| | | | | | Phase III for cryptococcal meningitis | NCT06666322 |
| Antifungals targeting intracellular metabolism | Olorofim | Oral and intravenous | 8−12 h | Dihydroorotate dehydrogenase (DHODH) | Phase III for invasive aspergillosis | NCT05101187 |
| | VL-2397 | Oral and intravenous | 4 h | Ferric ion transporter | Phase II for invasive aspergillosis | NCT03327727 |

The results of the latest clinical trials from https://clinicaltrials.gov/ (March 2025).

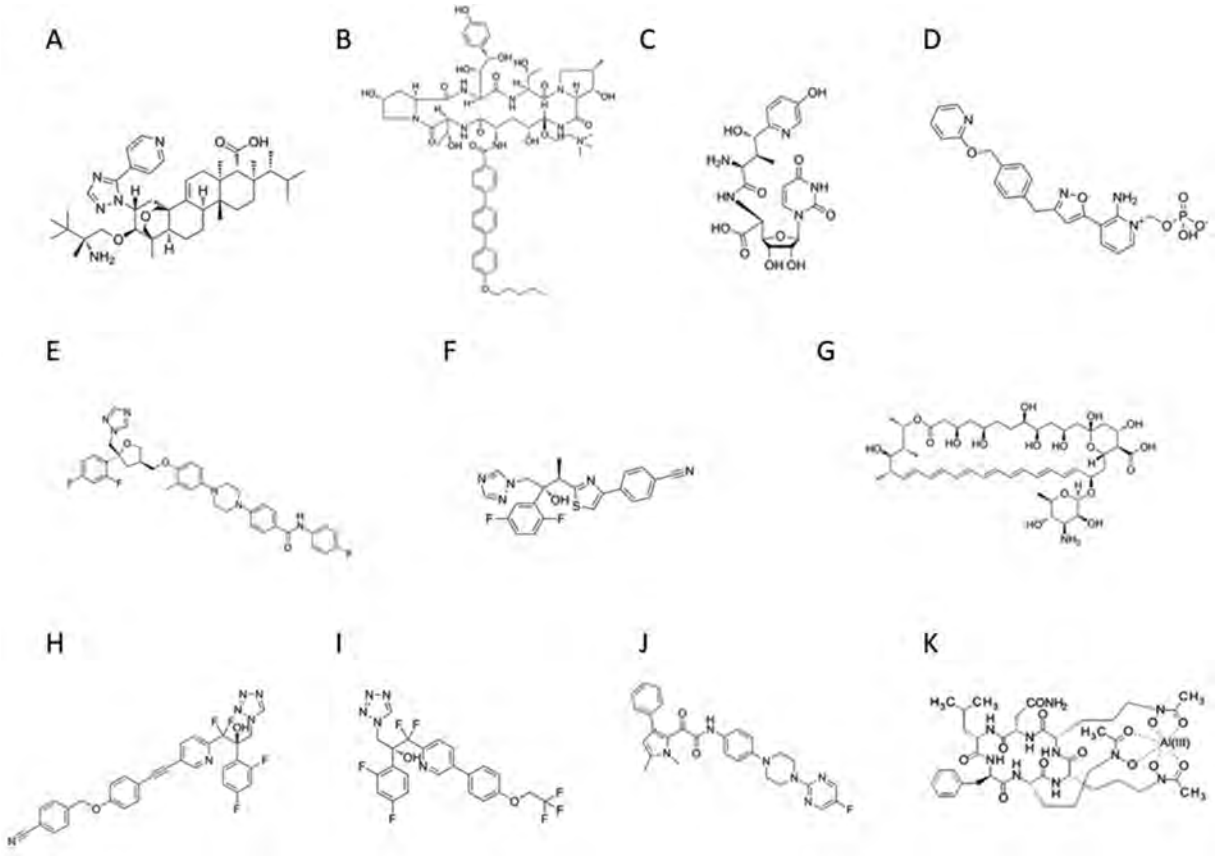


**Figure 3** Chemical structures of novel antifungals. (A) Ibrexafungerp ($C_{44}H_{67}N_5O_4 \cdot C_6H_8O_7$) is a triterpenoid derivative of the natural product enfumafungin; its pharmacological efficacy is dictated by the intrinsic triterpenoid framework together with specific functional group modifications. (B) Rezafungin ($C_{65}H_{88}N_8O_{19}$) is developed as a derivative of Echinocandin B and features a distinct fatty acyl side chain integrated into its cyclic peptide structure. (C) Nikkomycin Z ($C_{20}H_{25}N_5O_{10}$) is classified as a nucleoside-peptide antibiotic that couples an uracil nucleoside with a dipeptide chain. Notably, its AHA segment bears a high degree of structural similarity to the UDP moiety of UDP-*N*-acetylglucosamine (UDP-GlcNAc), enabling occupancy of the chitin synthase substrate binding site, while the HPHT extension further perturbs the enzyme's active site conformation, resulting in a dual inhibitory mechanism. (D) Fosmanogepix ($C_{18}H_{23}F_2N_3O_7P_2$) incorporates a bisphosphonate moiety, specifically a phosphonate oxybutoxy group, and functions as a prodrug that undergoes hydrolysis by alkaline phosphatase *in vivo* to yield the active compound manogepix (APX001A); this conversion releases a hydroxyl group that enhances cellular permeability. (E) Opelconazole ($C_{38}H_{37}F_3N_6O_3$) contains a 1*H*-1,2,4-triazole ring and shares the central pharmacophore with established triazole antifungals, while its long-chain hydrophobic substituent is designed to improve lipophilicity. (F) Isavuconazole ($C_{22}H_{17}F_2N_5OS$) features a 1*H*-1,2,4-triazole ring; however, the stereochemistry of its side chain (2*R*,3*R*) confers precise binding of the triazole moiety to the active site of fungal CYP51. (G) Encochleated Amphotericin B (MAT2203) ($C_{47}H_{73}NO_{17}$) primarily comprises amphotericin B, which is encapsulated within a nanoparticle shell formed by a phospholipid bilayer or a cholesterol complex that mimics the constituents of fungal cell membranes. (H) VT-1598 ($C_{31}H_{20}F_4N_6O_2$) employs a combination of a tetrazole ring and a pyridine group to achieve markedly higher affinity for fungal CYP51 relative to the corresponding human enzyme. (I) Oteseconazole ($C_{23}H_{16}F_7N_5O_2$) is structurally optimized with a tetrazole moiety, multiple fluorine substituents, and a refined stereochemical configuration, thereby enhancing its selectivity toward fungal CYP51. (J) Olorofim ($C_{28}H_{27}FN_6O_2$) incorporates essential structural features, including interconnected polycyclic elements and a moiety that selectively binds to the CBD region of dihydroorotate dehydrogenase (DHODH), resulting in potent and selective inhibition of the fungal enzyme. (K)VL-2397 ($C_{40}H_{59}AlN_{10}O_{13}$) is characterized by a cyclic hexapeptide backbone, an aluminum-chelating center, and siderophore-mimetic attributes, which collectively underlie its pharmacological activity.

by targeting a specific enzyme known as Fks1p, which is the catalytic unit of glucan synthase. In addition, they selectively inhibit an enzyme known as $\beta$-(1,3)-D-glucan synthase. Compared with conventional echinocandins, ibrexafungerp displays high oral bioavailability, extensive distribution, and minimal cross-resistance to echinocandin-resistant strains, primarily due to the selectivity of its binding site to the synthase[79,80] (Fig. 1).

Recent *in vitro* studies have demonstrated that ibrexafungerp has broad-spectrum antifungal effects on diverse *Candida* species. Notably, it retains substantial efficacy against strains harboring resistance-associated mutations in the Fks subunit[12,13,81]. Animal models of invasive candidiasis further corroborate its antifungal potency, with significant activity observed across multiple *Candida* morphotypes, including smooth and nearly smooth variants, as well as *Candida albicans*[82,83]. Moreover, ibrexafungerp has proven effective against *Candida auris*, a priority pathogen recognized by the World Health Organization for its multidrug-resistant profile[84,85]. In a rabbit neutropenia model, the combination of ibrexafungerp and isavuconazole had synergistic effects, significantly improving survival rates and reducing the fungal

load[86]. Further investigations have indicated that combining ibrexafungerp with amphotericin B offers a considerable advantage in treating drug-resistant CYP51A mutants[87] (Table 2).

In June 2021, the U.S. Food and Drug Administration (FDA) approved ibrexafungerp (BREXAFEMME®) for the indications of vulvovaginal candidiasis (VVC) and for reducing the incidence of recurrent VVC (RVVC)[88]. The effectiveness and safety of this drug have been confirmed through phase 2 and 3 clinical trials, where it was evaluated for the management of vulvovaginal candidiasis (VVC)[88,89]. According to the findings of the VANISH-306 trial, patients treated with ibrexafungerp demonstrated significantly higher rates of clinical resolution, fungal eradication, and overall improvement than those receiving a placebo[90,91] (Fig. 4, Table 3).

*3.1.1.2. Rezafungin.* As a second-generation echinocandin antifungal agent, rezafungin features a choline ether modification at the C5 ornithine site, significantly enhancing its chemical stability and solubility[92] (Fig. 3). This drug exerts its antifungal activity by binding to specific regions of Fks1p. By interfering with the transfer of UDP-glucose to the cell wall, rezafungin effectively inhibits the synthesis of $\beta$-1,3-glucan[93]. Although it shares the same binding site as first-generation echinocandins do, its structural modifications enhance interactions with the lipid microenvironment, potentially allowing for a tighter binding that directly disrupts enzyme−substrate interactions, specifically between Fks1p and UDP-glucose[94] (Fig. 1). In contrast, first-generation echinocandins act primarily by inhibiting enzyme conformational changes. This mechanistic difference grants rezafungin superior inhibitory activity against resistance-associated mutations, such as Fks1p mutants[95]. Its optimized solubility further enhances its distribution in biofilms and deep tissues, such as the lungs and central nervous system, thereby improving its efficacy in eliminating cryptic infection foci[96].

*In vitro* studies have validated that rezafungin displays potent antifungal activity against a broad spectrum of pathogens, including strains resistant to standard therapies that frequently pose significant treatment challenges[13,14,94]. Animal studies have demonstrated its significant inhibitory effects against *Candida* spp. and *Aspergillus* spp., although its activity against *Cryptococcus* spp. is less pronounced[97-100]. Rezafungin offers distinct pharmacokinetic advantages over first-generation echinocandins[101]. Notably, it undergoes minimal biotransformation in liver microsomes and hepatocytes and has a reduced impact on cytochrome P450 (CYP450) enzymes, significantly lowering the risk of drug−drug interactions. These characteristics make it well suited for complex dosing regimens, particularly in multidrug therapy settings[102,103] (Table 2).

Owing to these favorable properties, rezafungin was granted orphan drug status in both the United States and the European Union in 2023, specifically for treating candidaemia and invasive candidiasis in adults with limited or no alternative treatment options. The phase III ReSTORE trial demonstrated that rezafungin provided comparable efficacy and safety to caspofungin, further supporting its potential for clinical use[104] (Fig. 4, Table 3).

## 4. Inhibitors of chitin synthase

Chitin, a polysaccharide[105], consists of *N*-acetylglucosamine (GlcNAc) monomers and constitutes an essential structural element of the fungal cell wall[106]. Chitin biosynthesis is governed by chitin synthase, an enzyme that facilitates the assembly of uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc), which functions as a sugar donor. This enzymatic activity promotes the establishment of $\beta(1\rightarrow4)$ glycosidic bonds, thereby enabling the translocation of the newly synthesized polysaccharide across the cellular membrane *via* transmembrane channels. Once transported, polysaccharides are integrated into the cell wall matrix[106]. Chitin synthase inhibitors typically disrupt chitin biosynthesis through two main mechanisms. These inhibitors can either compete for the UDP−GlcNAc binding site or bind directly to the enzyme, triggering a conformational change that further inhibits chitin synthesis. This dual mode of action enhances the specificity and potency of these inhibitors[107]. Given that chitin is absent in

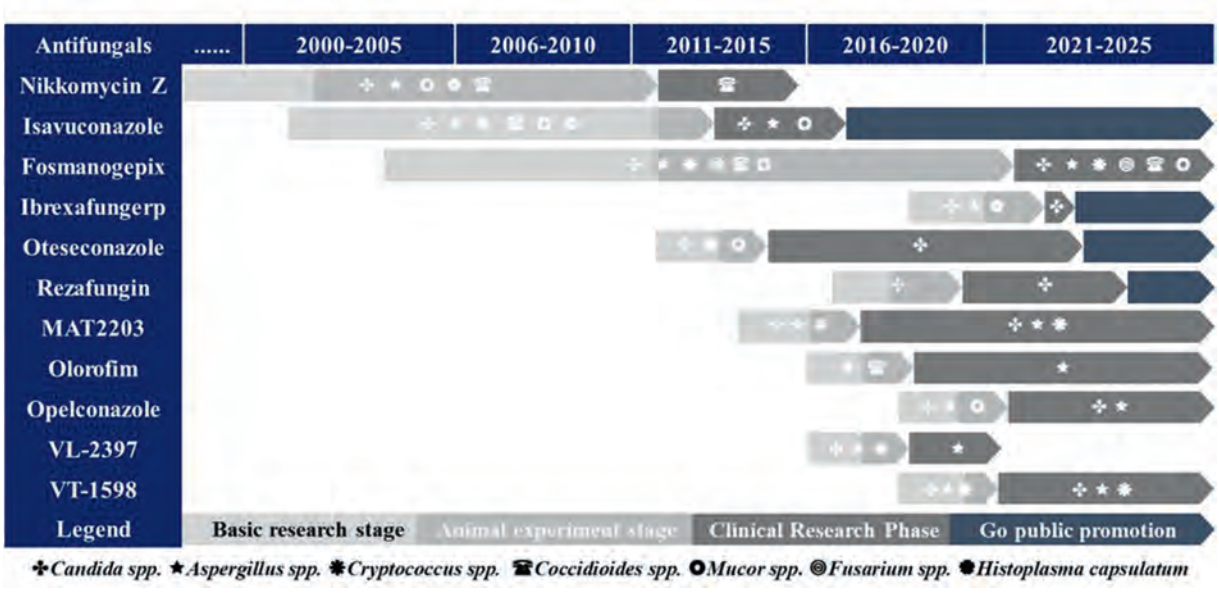


**Figure 4** Development of novel antifungals. The development process of new antifungal drugs currently in clinical trials, including basic research stage, animal experiment stage, clinical trial stage and official marketing stage.

both plants and vertebrates, its biosynthetic pathway is considered an ideal target for the development of antifungal agents, as are bactericides and insecticides[106,108].

### 4.1. Nikkomycin Z

Nikkomycin Z (NikZ) is a secondary metabolic compound synthesized by the actinomycete *Streptomyces tendae* (Fig. 3). The chemical structure of NikZ comprises two principal components: a UDP-like aminohexane carboxylic acid (AHA) segment and a distinctive 4-hydroxypyridine-homothreonine (HPHT) peptidyl segment[109]. The AHA portion of NikZ is structurally similar to the UDP moiety of UDP−GlcNAc, whereas the HPHT portion is capable of penetrating deeply into the substrate channel of the enzyme, thereby interfering with the extension of the chitin chain. This dual mechanism of action enables Nikkomycin Z to effectively inhibit chitin synthesis, thereby hindering fungal cell wall formation[108] (Fig. 1).

*In vitro* and *in vivo* experiments confirmed that Nikkomycin Z exhibits robust antifungal activity against a broad spectrum of pathogens. The compound demonstrates efficacy against dimorphic fungi-namely, *Histoplasma capsulatum*, *Coccidioides* spp., and *Blastomyces dermatitidis*-as well as against additional organisms such as *Sporothrix* spp., *Candida albicans*, and *Aspergillus* spp.[15-17]. In murine models, Nikkomycin Z achieved superior therapeutic outcomes to those of azole antifungals and amphotericin B for the treatment of systemic coccidioidomycosis and blastomycosis, and it further displayed fungicidal effects within pulmonary tissues[17,110-112]. Moreover, combination therapy involving Nikkomycin Z has yielded promising results: coadministration with echinocandins produces a synergistic antifungal effect against *Aspergillus fumigatus*[113,114] while pairing it with fluconazole or itraconazole enhances its efficacy against multiple *Candida* species[115] (Table 2).

The initial phase of clinical trials for Nikkomycin Z has been completed, revealing that the drug is generally well tolerated when it is administered as a single oral dose to healthy volunteers, with no dose-related adverse effects reported up to 2000 mg[116,117]. However, a phase II trial for the treatment of coccidioidomycosis was prematurely halted because of recruitment challenges and insufficient funding (ClinicalTrials.gov NCT00614666). Despite this setback, the unique mechanism of action and promising antifungal activity of Nikkomycin Z position it as a potential new therapeutic option. It is expected that further clinical research and refinement will lead to its eventual integration into clinical practice (Fig. 4, Table 3).

## 5. Inhibitors of glycosylphosphatidylinositol (GPI)

GPI-anchored proteins are essential constituents of the fungal cell wall and are anchored to the cell wall by a special molecule called glycosylphosphatidylinositol. These proteins are crucial for several fungal processes, such as adhesion, invasion, biofilm formation, and maintaining cell wall integrity[118]. The synthesis of glycosylphosphatidylinositol (GPI)-anchored proteins is a multistep process in which the enzymes Gwt1 and Mcd4 serve as critical rate-limiting factors. Gwt1 mediates the assembly and modification of GPI structures by transferring precursor molecules to lipid-associated regions[119], whereas Mcd4 further refines these molecules to ensure their proper functionality. Inhibition of these pivotal enzymes disrupts the production of GPI-anchored proteins, resulting in a disorganized cell wall architecture that compromises fungal virulence and survival[119-122]. Given the ubiquitous presence and diverse roles of GPI-anchored proteins in fungal cells[118], targeting this biosynthetic pathway represents a promising strategy for the development of novel antifungal therapies.

### 5.1. Fosmanogepix (APX001)

Fosmanogepix (APX001) is a multifaceted antifungal compound provided in both oral and intravenous formulations. As a prodrug, it is rapidly metabolized by phosphatases into its active moiety, manogepix (Fig. 3). This active agent exerts its antifungal effects by interfering with the glycosylphosphatidylinositol (GPI) anchor biosynthesis pathway, chiefly through inhibition of the Gwt1 enzyme, a critical rate-limiting factor in fungal cells[123,124] (Fig. 1). Importantly, manogepix does not affect proteins encoded by the human homolog of *GWT1*, *PIGW*[122,125]. This significantly minimizes the potential for systemic toxicity.

*In vitro* evaluations have revealed the extensive antifungal efficacy of Manogepix against a wide array of fungal pathogens, such as *Candida* spp., *Cryptococcus* spp., *Coccidioides* spp., *Aspergillus* spp., and other less common molds[18-20,125-127]. In animal models, Fosmanogepix has been shown to significantly increase survival rates while decreasing the fungal load in the brains of mice with disseminated *Candida auris* infections. The effectiveness of this drug has also been demonstrated in models of *Candida* endophthalmitis and hematogenous meningoencephalitis[127]. Additionally, combination therapy with manogepix and liposomal amphotericin B has resulted in a synergistic effect, as evidenced by reduced fungal burdens in the lungs of patients with invasive pulmonary aspergillosis and improved survival in individuals infected with trichothecenes. Moreover, the fungal load was significantly decreased in both lung and brain tissues[128]. In addition to Fosmanogepix, several analogs that target the Gwt1 enzyme, such as G884, G365, and gepinacin, have been developed, broadening the potential for therapeutic intervention in fungal infections[129] (Table 2).

The results of phase II clinical trials revealed that azole-resistant *Aspergillus*, echinocandin-resistant *Candida*, and rare fungi such as *Fusarium* and *Scedosporium* exhibited *in vitro* activity (MIC range 0.002−0.03 mg/L) (ClinicalTrials.gov ID NCT04240886, NCT04148287). Currently, Fosmanogepix has entered a phase III clinical trial (ClinicalTrials.gov ID NCT05421858). Furthermore, the maturation of GPI-anchored proteins requires an additional pivotal enzyme, Mcd4, which serves as an indispensable ethanolamine phosphotransferase in GPI modification. Inhibition of Mcd4 activity also results in disruption of the fungal cell wall structure, which in turn reduces virulence and viability[130]. Novel inhibitors that are currently being developed to target Mcd4 include M743 and M720, which are also considered to have high potential for use in antifungal therapies[130] (Fig. 4, Table 3).

### 5.2. Jawsamycin (FR-900848)

Jawsamycin has been recognized as the pioneering compound capable of inhibiting the fungal UDP-GlcNAc phosphatidylinositol transfer complex. This inhibition disrupts fungal cell wall stability and functionality by blocking the glycosylphosphatidylinositol (GPI) biosynthesis pathway, a process driven by the suppression of the fungal UDP-glycosyltransferase subunit Spt14/Gpi3[131] (Fig. 1). Notably, Jawsamycin exhibits

strong selectivity for mammalian homologous enzymes, contributing to its favorable safety profile in treating fungal infections[131].

*In vitro* studies have revealed that Jawsamycin has broad-spectrum antifungal activity, with particular efficacy against *Mucor*, *Fusarium*, and *Trichosporon* spp.[132]. Microscopic examination revealed that Jawsamycin-treated *Rhizopus oryzae* spores experienced substantial swelling and leakage of their cellular contents, indicative of the potent fungicidal effect of Jawsamycin[132]. *In vivo*, oral administration of Jawsamycin resulted in a significant increase in the survival rates of mice with invasive pulmonary mucormycosis, further confirming its therapeutic potential. Safety assessments revealed that Jawsamycin did not exhibit toxicity in various human cell lines (HEK293T, HCT116, HEPG2, and K562) at concentrations up to 50 μmol/L, underscoring its high therapeutic index and safety[132]. These promising properties position Jawsamycin as a valuable candidate for treating *Mucoromycete* infections. However, the identification and development of antifungal compounds remain in the early stages of investigation.

### 5.3. Nagilactone E

Nagilactone E, a demethylated diterpene bilactone isolated from *Pinus rosa-sinensis*, has been shown to exhibit antifungal properties against both nonpathogenic *Saccharomyces cerevisiae* and pathogenic fungi, including *Candida albicans* and *Pseudomonas ovale*. Its activity is linked to the disruption of cell wall integrity, particularly through the inhibition of $\beta$-1,3-glucan synthase activity[133]. Notably, when combined with phenylpropanoid compounds such as anisodamine and isosafrole, Nagilactone E enhances the antifungal potency of these agents against *Saccharomyces cerevisiae* and *Candida albicans*. These findings suggest that Nagilactone E holds promise as a potential candidate for the development of novel antifungal therapies[134].

Additionally, a range of naturally sourced compounds have promising inhibitory effects on critical enzymes associated with fungal cell wall construction. Specifically, poacic acid obtained from the lignocellulosic hydrolysate of Gramineae, along with the phenolic macrocyclic compound bis-plagiochin E from peanut extracts[135,136], the anthraquinone derivative rhubarbine isolated from rhubarb roots and rhizomes[137], and *trans-cinnamaldehyde*[138], a principal constituent of camphor bark essential oil, have been recognized as inhibitors of $\beta$-glucan synthase. The antifungal action appears to stem from interference with the production of vital cell wall elements, $\beta$-(1,3)-D-glucan and chitin-as well as from interactions with structural molecules, including mannan proteins and glucosylceramides, ultimately disrupting the integrity of the fungal cell wall.

By inhibiting the synthesis of key structural components such as $\beta$-1,3-glucan, chitin, and glycosylphosphatidylinositol (GPI)-anchored proteins, novel antifungal agents that target the fungal cell wall exhibit high efficacy and low toxicity. Since these components are absent in mammalian cells, such agents demonstrate high selectivity, significantly reducing toxicity to the host. However, several limitations remain. Some agents, such as nikkomycin Z, have been discontinued owing to difficulties in patient recruitment and funding shortages during clinical trials, restricting their further development. In addition, resistance remains a major challenge, particularly in mutant strains that target $\beta$-1,3-glucan synthase. With respect to potential targets, future research may further explore the biosynthetic pathways of other essential fungal cell wall components, such as mannoproteins and glucosylceramides. Additionally, natural compounds, including terpenoids and phenolic compounds, represent promising sources for novel antifungal agents and may provide new insights into their unique mechanisms of action and broad-spectrum activity.

### 5.4. Antifungals targeting cell membranes

#### 5.4.1. Inhibitors of CYP51

Fungal cell membranes consist predominantly of phospholipids, sphingolipids, and sterols that form a robust matrix supporting a variety of functional proteins. In fungal organisms, ergosterol serves as the principal sterol, contrasting sharply with cholesterol, which is the main sterol in human cell membranes[139]. The conversion of lanosterol to ergosterol is catalyzed by lanosterol-14$\alpha$-demethylase (CYP51), an enzyme encoded by the *ERG11* gene. Conventional azole antifungal agents exert their activity by inhibiting CYP51, thereby impeding ergosterol biosynthesis and causing the buildup of harmful sterol intermediates that disrupt fungal cell proliferation[55]. However, owing to the incorporation of imidazole or triazole moieties in their structures, these agents may also inadvertently affect the human CYP51 homolog, leading to undesirable adverse effects. In response, recent innovations have concentrated on developing antifungal compounds with increased selectivity for fungal membranes. Such next-generation therapies, refined through targeted molecular design and advanced drug delivery strategies, minimize off-target effects on human CYP51 and offer improved pharmacokinetic profiles, ultimately increasing their clinical efficacy in the treatment of invasive fungal infections.

*5.4.1.1. Opelconazole (PC945).* Opelconazole (PC945) is a highly effective, broad-spectrum triazole antifungal agent (Fig. 3). It exerts its action by specifically targeting lanosterol 14$\alpha$-demethylase (CYP51A1), the critical enzyme responsible for converting lanosterol into ergosterol. Unlike traditional systemic triazoles, opelconazole is formulated for inhalational delivery, thereby enabling high local concentrations in the lungs while minimizing systemic exposure. This localized administration markedly reduces toxicity risks and limits drug−drug interactions mediated by the CYP450 enzyme system[140,141] (Fig. 1).

*In vitro* studies have confirmed that opelconazole exhibits robust antifungal activity against a diverse range of *Aspergillus* species[142]. Furthermore, the combination of opelconazole with systemic triazoles was found to enhance antifungal effects, providing sustained and effective inhibition in both an *in vitro* human alveolar bilayer model and a neutropenic immunocompromised mouse model[143,144]. Opelconazole was rapidly absorbed by both target and nontarget cells, maintaining prolonged antifungal activity against fungal hyphae and bronchial cells. In a neutropenic mouse model infected nasally with *Aspergillus fumigatus*, topical application of opelconazole resulted in a strong antifungal response in the lungs[141] (Table 2).

The FDA has conferred designations including Orphan Drug, Fast Track, and Qualified Infectious Disease Product status on opelconazole. A phase III study (OPERA-T, ClinicalTrials.gov ID NCT05238116) is presently assessing its therapeutic potential and safety in patients with invasive pulmonary aspergillosis (IPA) who

have not responded to conventional antifungal regimens. The combination of favorable preclinical outcomes and these ongoing clinical evaluations highlights the promise of opelconazole as a novel topical intervention for IPA, thereby expanding treatment possibilities for this challenging condition (Fig. 4, Table 3).

*5.4.1.2. Isavuconazole.* Isavuconazole is a broad-spectrum triazole antifungal agent characterized by its molecular structure, which includes an *N*-(3-acetoxypropyl)-*N*-methylamino-carboxymethyl side chain (Fig. 3). This structure enables the drug to bind specifically to fungal CYP51, disrupting fungal cell membrane integrity and inhibiting fungal growth[145] (Fig. 1).

*In vitro* and *in vivo* investigations consistently indicate that isavuconazole has robust antifungal activity against a broad spectrum of yeast and mold species. Tested organisms include various *Aspergillus, Fusarium, Candida, Trichoderma, Cryptococcus*, and *Nigrospora* spp., in addition to other filamentous fungi[25-27,146-149]. Notably, in an *Aspergillus flavus* infection model, isavuconazole demonstrated pronounced antifungal efficacy. In a murine model of disseminated aspergillosis in immunocompetent hosts, the therapeutic effect against both wild-type *Aspergillus fumigatus* strains and azole-resistant CYP51A variants was observed to depend on exposure duration and the minimum inhibitory concentration (MIC)[147]. Furthermore, in a neutropenic mouse model of endotracheal infection, a high-dose regimen of isavuconazole (215 mg/kg administered three times daily) substantially prolonged survival in animals pretreated with cyclophosphamide and cortisone acetate while markedly reducing pulmonary fungal burdens[150] (Table 2).

The FDA and the European Medicines Agency (EMA) have approved isavuconazole to treat severe fungal infections. This indication covers infections caused by *Aspergillus* species-including invasive pulmonary aspergillosis, and those caused by *Candida* species, such as invasive candidiasis[146,151] (Fig. 4, Table 3).

*5.4.1.3. VT-1598 and oteseconazole (VIVJOA®, VT-1161).* The latest generations of azole antifungal agents, VT-1161 and VT-1598, demonstrate enhanced specificity for the fungal lanosterol 14$\alpha$-demethylase (CYP51) by substituting the conventional triazole structure with a tetrazole group[152,153] (Fig. 3). This structural modification not only improves drug selectivity but also significantly reduces the inhibitory effects of drugs on human CYP450 enzymes (*e.g.*, CYP3A4, CYP2C9, and CYP2C19), thus minimizing the potential for drug−drug interactions[152-154] (Fig. 1).

*In vitro* studies have shown that VT-1598 has a broad antifungal spectrum, effectively targeting yeasts such as *Candida* and *Cryptococcus* species, molds such as *Aspergillus* species, and endemic fungi[30,155-158]. In mouse models of central nervous system infections, VT-1598 has been shown to increase survival while reducing fungal loads in the kidneys and brain during coccidioidomycosis[159] and cryptococcosis[160], thereby improving overall prognosis[161]. Additionally, VT-1598 has demonstrated efficacy against both fluconazole-sensitive and fluconazole-resistant *Candida* strains isolated from chronic mucocutaneous candidiasis patients[157,161] (Table 2). Clinical trials of VT-1598, currently in phase I (NCT04208321), have not reported any severe adverse events or instances of early trial termination (Fig. 4, Table 3).

VT-1161 has a high binding affinity for *Candida albicans* CYP51, with a $K_D$ value of $\leq$39 nmol/L[55], which is more than 2000 times greater than its affinity for the human homodimer[154]. As a result, VT-1161 shows potent activity against *Candida albicans*, *Candida smoothii*, and *Candida near-smoothii* both *in vitro* and *in vivo*[13,31]. The drug is also effective against fluconazole- or echinocandin-resistant strains and has demonstrated efficacy in treating coccidioidomycosis in mice[154,162] (Table 2). Numerous clinical trials have confirmed the efficacy and safety of VT-1161 for managing recurrent vulvovaginal candidiasis (RVVC) and vulvovaginal candidiasis (VVC), leading to its FDA approval in April 2022 (clinicaltrials.gov: NCT03840616, NCT03562156, and NCT03561701)[163] (Fig. 4, Table 3).

## 6. Inhibitors of sphingolipid synthesis

Sphingolipids are among the key components of the fungal cell membrane lipid bilayer and, together with ergosterol, form "lipid raft" microdomains that regulate the localization and function of membrane proteins. The unique structural relationship between the hydrophobic sphingoid base and the hydrophilic head group (*e.g.*, phosphocholine) endows the cell membrane with dynamic equilibrium, thereby assisting fungi in adapting to environmental changes such as osmotic pressure and temperature fluctuations[164]. Sphingolipid synthesis inhibitors are a class of antifungal agents that disrupt fungal cell membrane integrity or interfere with signal transduction by targeting key enzymes in the sphingolipid metabolic pathway (*e.g.*, inositol phosphorylceramide [IPC] synthase)[165,166]. However, the limited elucidation of the protein structures of these sphingolipid-synthesizing enzymes has somewhat constrained structure-based drug design and high-throughput screening. Although current inhibitors (such as khafrefungin and rustmicin) exhibit potent antifungal activity, their chemical stability and drug-like properties still require further optimization.

### 6.1. Aureobasidin A

Derived from the filamentous fungus *Aureobasidium pullulans* strain R106, aureobasidin A (AbA) is a cyclic depsipeptide antibiotic. AbA exerts its antifungal action by targeting inositol phosphorylceramide synthase (IPC synthase)[167], thereby interrupting the conversion of ceramide into inositol phosphorylceramide and reducing sphingolipid synthesis. This sphingolipid insufficiency compromises the structural integrity of fungal cell membranes, ultimately leading to cellular lysis and death[168].

Extensive experimental evidence has demonstrated that aureobasidin A has potent inhibitory effects on a broad spectrum of pathogenic fungi, including *Candida albicans*, *Candida glabrata*, *Aspergillus nidulans*, and *Aspergillus niger*[169,170]. Preclinical studies in murine models have validated its efficacy in treating systemic candidiasis[171,172]. Moreover, combining aureobasidin A with amphotericin B (AmB) has produced superior therapeutic outcomes relative to conventional treatment regimens for cryptococcal meningitis in mice[169,173].

## 7. Inhibitors of ergosterol

### 7.1. Encochleated amphotericin B (MAT2203)

Amphotericin B (AmB) is a polyene antifungal agent (Fig. 3). Its action is mediated through a selective interaction with ergosterol indispensable sterol in fungal membranes-which leads to the formation of transmembrane channels. The efflux of intracellular

constituents ultimately disrupts cellular homeostasis, resulting in fungal cell death (Fig. 1). However, its clinical use has been significantly limited, mainly due to its high toxicity (especially nephrotoxicity) and complex mode of administration involving slow intravenous injection[174,175]. MAT2203 is an innovative oral formulation of amphotericin B that employs nanocrystal encapsulation (Encochleation), which significantly improves the stability and bioavailability of the drug[176-178]. This modification facilitates the oral administration of MAT2203, thereby enabling the efficacious management of fungal infections. In addition, it facilitates ease of administration and mitigates the risk of associated toxicity in contrast to conventional parenteral formulations of amphotericin B.

Animal studies have demonstrated that MAT2203 has efficacy comparable to that of conventional amphotericin B deoxycholate (AMB-d) in the treatment of invasive candidiasis, aspergillosis, sporotrichosis, and cryptococcosis, but has significantly reduced toxicity[179-183]. In a murine model of disseminated candidiasis, MAT2203, when administered orally, achieved a 100% survival rate at doses ranging from 0.5 to 20 mg/kg/day. The drug was also effective in decreasing fungal colonization in infected organs in a dose-dependent manner[180,182]. At a low dose of 0.5 mg/kg/day, MAT2203 completely rescued mice infected with *Candida* cells and reduced fungal colony counts in the kidneys and lungs by approximately two logs[182]. A higher dose of 2.5 mg/kg/day resulted in a more pronounced effect, reducing kidney colony counts by more than three logs and eliminating yeast cells from the lungs. These findings further highlight the promising therapeutic potential of MAT2203 in treating systemic fungal infections with lower toxicity than AMB-d[182] (Table 2).

MAT2203 has undergone phase III clinical evaluation and has demonstrated superior antifungal efficacy[184]. Its performance is comparable to that of standard intravenous amphotericin B in the treatment of invasive candidiasis and aspergillosis. Furthermore, the oral formulation of MAT2203 significantly reduces the risk of nephrotoxicity and other adverse treatment-related events[185] (Fig. 4, Table 3).

### 7.2. AM2-19

AM2-19 is an innovative antifungal agent engineered through the chemical optimization of amphotericin B (AmB) (Fig. 3). This compound selectively binds ergosterol in fungal cell membranes while exhibiting minimal activity against cholesterol in human cell membranes[186]. Its high selectivity allows for the continuous removal of ergosterol from fungal membranes, which function much like a sponge and ultimately lead to fungal cell death. Consequently, AM2-19 has potent antifungal efficacy while minimizing nephrotoxic effects on human kidney cells[29]. This mechanism effectively overcomes the major limitation of conventional amphotericin B, namely, high nephrotoxicity, while improving its efficacy (Fig. 1).

AM2-19 has been demonstrated to exhibit broad-spectrum antifungal activity against more than 500 pathogenic fungal strains, including a multitude of variants resistant to existing antifungal medications. *In vitro* studies have demonstrated that AM2-19 has an excellent safety profile in human blood and kidney cell environments. *In vivo* experiments in mouse models were conducted to evaluate the therapeutic efficacy of AM2-19 in three common recalcitrant fungal infections. The results demonstrated that AM2-19 was not only efficacious but also significantly less toxic than conventional treatments[29] (Table 2).

AM2-19 was approved to enter phase I clinical trials in 2023 (ClinicalTrials.gov IDNCT06666322), during which its safety and antifungal activity in humans were evaluated. It is anticipated that this innovative pharmaceutical agent will offer a novel therapeutic avenue for individuals afflicted with fungal infections that are refractory to conventional antifungal therapies while concomitantly diminishing the incidence of associated adverse effects (Fig. 4, Table 3).

## 8. Antifungal compounds that are still in the early stages of research

### 8.1. Selenium-containing azole derivatives

In a recent study, a novel type of antifungal agent was identified: a selenium-containing azole derivative, designated compound **B01**. This compound inhibits fungal ergosterol synthesis by occupying the hydrophobic channel of the CYP51, thereby significantly enhancing its antifungal activity. *In vitro* experiments demonstrated that **B01** is 4- to 64-fold more potent than fluconazole and exhibits significant bactericidal activity against fluconazole-resistant fungal strains. Furthermore, B01 displays high metabolic stability, low cytotoxicity, and minimal risk of hemolysis, which provides a favorable foundation for its potential clinical utilization[187].

*In vivo* investigations have indicated that compound **B01** exhibits robust antifungal activity in therapeutic applications. In a murine model of disseminated *Candida albicans* infection, the intraperitoneal administration of **B01** led to a significant decrease in renal fungal burden, thereby underscoring its potential as an effective antifungal agent. Concurrently, the compound exhibited minimal toxicity in acute and subacute toxicity tests[187]. These properties render selenium-containing azole derivatives an emerging area of interest within the field of antifungal drug development, particularly in the context of treating drug-resistant strains.

### 8.2. 4H-Pyrano[3,2-c]pyridine derivatives

4*H*-Pyrano[3,2-*c*]pyridine derivatives constitute a novel group of inhibitors that target sterol 14$\alpha$-demethylase (CYP51), which are engineered to optimize the suppression of fungal enzymes[188]. Prior research successfully synthesized 34 novel derivatives within this class through the application of rational structural design and advanced synthetic methodologies. These compounds bind stably to the hydrophobic cleft of CYP51, thereby inhibiting its activity. *In vitro* experiments demonstrated that these compounds significantly inhibited sterol 14$\alpha$-demethylase even at relatively low concentrations. Fungicidal assays revealed that most 4*H*-pyrano [3,2-*c*]pyridine derivatives demonstrate potent inhibition at a concentration of 16 μg/mL. In these experiments, significant antifungal effects were observed against clinically relevant pathogens, notably *Penicillium fingerlingi* and *Fusarium acuminatum*[188].

### 8.3. JIB-04 and its derivatives

H3K27me3, a marker of transcriptional repression in epigenetics, suppresses gene expression at specific loci through mechanisms mediated by the Polycomb Repressive Complex (PRC). In fungi, the dynamic regulation of H3K27me3 is critical for environmental

adaptation[189]. For example, under host immune pressure or antifungal drug treatment, demethylases modulate the expression of virulence factors and drug resistance genes by removing H3K27me3, thereby increasing fungal survival[190].

JIB-04 is a novel inhibitor that specifically targets the fungal Jumonji H3K27me3 demethylase[191,192]. The experimental data indicate that JIB-04 markedly suppresses the enzyme's activity in *Cryptococcus neoformans* cells, thereby impeding ergosterol synthesis and eliciting strong antifungal effects against *Cryptococcus* in both *in vitro* and *in vivo* models. Moreover, treatment with JIB-04 significantly downregulated critical virulence determinants, including mechanisms underlying biofilm formation, melanin synthesis, capsule production, and cell surface hydrophobicity. Consequently, this compound has been validated as an effective antifungal agent for managing cryptococcal meningitis, and the Jumonji histone demethylase has emerged as a promising target for novel antifungal drug development. Although JIB-04 exhibits robust antifungal potency across a broad range of pathogens, its clinical utility is hampered by poor aqueous solubility, an imprecise structure−activity relationship (SAR), and insufficient pharmacological specificity[192]. To address these limitations and enhance both antifungal efficacy and pharmacokinetic performance, researchers have developed structural optimization strategies. Through the design and synthesis of various derivatives, compound **A4** was identified as a promising candidate that exhibits robust antifungal potency alongside a clearly defined mechanism of action. Empirical studies have revealed that **A4** effectively inhibits the growth of *Cryptococcus neoformans* and *Candida auris*, with minimum inhibitory concentrations (MICs) of 0.5 and 0.125 μg/mL, respectively, thereby surpassing the efficacy of the standard antifungal agent fluconazole (FLC). In addition, **A4** has potent fungicidal effects, with minimum fungicidal concentrations (MFCs) of 8 μg/mL for *C. neoformans* and 64 μg/mL for *C. auris*. Mechanistic analyses indicate that A4 not only impedes biofilm formation and capsule synthesis in *Cryptococcus* but also disrupts the cellular architecture by compromising the integrity of both the cell membrane and the cell wall[192].

### *8.4. Scyampcin44-63*

A novel antimicrobial peptide, Scyampcin 44-63, was isolated from the mud crab *Scylla paramamosain*[193]. Studies have consistently demonstrated that this peptide effectively suppresses both the proliferation of planktonic cells and biofilm formation in *Candida albicans*. Moreover, scyampcin 44-63 exhibits excellent safety profiles, as it displays no cytotoxicity toward mammalian cells or murine erythrocytes. The peptide's antifungal activity is hypothesized to be mediated by multiple mechanisms, including the inhibition of ergosterol biosynthesis, the induction of autophagic cell death and apoptosis, and the disruption of the fungal cell cycle. In a murine model of vaginal candidiasis, intravaginal administration of scyampcin 44-63 led to a significant reduction in the *Candida albicans* burden and a pronounced decrease in pseudohyphal formation within the vaginal mucosa[193].

### *8.5. Allicin*

Allicin, a naturally occurring compound that is produced through a catalytic reaction between allicin extracted from garlic and alliinase, has been shown to possess a variety of antimicrobial properties[193,194]. Its mechanism of action is primarily through the penetration of fungal cell membranes and organelle membranes (*e.g.*, mitochondria), which results in organelle destruction and the induction of cell death[195]. Transcriptomic analyses have revealed that the target genes of allicin correlate with several biological pathways intrinsic to fungal cell membranes. These include but are not limited to mismatch repair, GPI-anchored biosynthesis, the mitogen-activated protein kinase (MAPK) signaling pathway, and the phosphatidylinositol signaling system[196].

Allicin exhibited concentration-dependent anti-*Cryptococcus* activity both *in vitro* and *in vivo*. Furthermore, it has demonstrated notable antifungal efficacy against a diverse array of pathogenic fungi, including *Candida*, *Coccidioides*, *Trichophyton*, *Cryptococcus*, *Aspergillus*, red yeast, and *Fusarium acuminatum*[195-199]. In a murine model, allicin (8 mg/kg) demonstrated a comparable anti-novel cryptococcal effect to that of fluconazole (FLU, 20 mg/kg) and exhibited a synergistic therapeutic effect against novel *Cryptococcus* when combined with amphotericin B (AmB)[196].

Novel antifungal agents that target the fungal cell membrane have demonstrated significant potential in the treatment of invasive fungal infections, showing promise for enhanced efficacy, reduced toxicity, and overcoming resistance; however, further research and clinical validation are needed. In addition to conventional targets, potential membrane-associated targets warrant attention, such as two-component signal transduction proteins (for example, the histidine kinases Sln1 and Hik1[200)], enzymes involved in membrane lipid remodeling (such as phospholipases[201], and fungal-specific membrane transporters such as the ergosterol transporters Aus1 and Pdr11[202]. Furthermore, targets related to virulence factors and host−pathogen interactions deserve further exploration. Membrane-bound virulence factors, such as those of the Als family in *Candida*, play critical roles in fungal colonization and infection[203]. Strategies aimed at these targets could directly diminish fungal invasiveness and effectively prevent early colonization during infection, thereby offering new avenues for antifungal therapy.

## 9. Antifungal compounds that target mycelia and biofilms

The capacity of fungal hyphae to proliferate and invade is pivotal to their pathogenicity. They not only facilitate fungal dissemination and colonization of the host but also increase the invasiveness of the fungus into host tissues, thereby precipitating further tissue damage and infection. In contrast, fungal biofilms have been demonstrated to impede the penetration and distribution of antifungal drugs significantly. This is achieved through the formation of extracellular matrix barriers, the upregulation of drug efflux pump gene expression, the reduction of cell permeability, the slowing of cell growth, and the possible expression of drug resistance genes[204,205]. The net result of these processes is the formation of a drug-tolerant biofilm, which presents a significant challenge to the efficacy of antifungal therapy[206]. Some of the antifungal drugs currently under investigation have the potential to inhibit mycelial growth and development, as well as biofilm formation, by modulating the expression of relevant genes or enzyme activities, thereby exerting antifungal effects.

### *9.1. 3,2′-DHF*

3,2′-Dihydroxyflavone (3,2′-DHF), a rare dihydroxyflavonoid, is primarily isolated from the tropical plant *Marsdenia tinctorial*[207]. Experimental evidence indicates that 3,2′-DHF exerts marked antibiofilm effects against *Candida albicans* at concentrations

within the low microgram-per-millilitre range[196]. Subsequent investigations revealed that this compound significantly curtails the development of *C. albicans* biofilms and mycelial growth by downregulating several mycelial-specific genes, such as *ECE1* (encoding a mycelial-specific protein), *HWP1* (a mycelial cell wall protein), and *UME6* (a filament-specific transcription factor)[208].

### 9.2. Nepodin

When isolated from rhubarb root, the compound nepodin significantly inhibited *Candida smoothii*, *Candida near-smoothii*, *Staphylococcus aureus*, and *Acinetobacter baumannii*. Its antifungal activity is achieved by suppressing the expression of genes involved in hyphal development and biofilm formation-namely, *ECE1*, *HGT10*, *HWP1*, and *UME6*-while concurrently upregulating specific transporter genes, such as *CDR4*, *CDR11*, and *TPO2*, which are implicated in biofilm regulation[208]. Furthermore, nepodin exhibited robust antibiofilm, antifilament, and antitoxic properties against fluconazole-resistant *Candida albicans* strains and polymicrobial biofilms. In a nematode infection model, treatment with nepodin substantially reduced the virulence of *C. albicans* while maintaining low cytotoxicity toward both nematode and mammalian cell lines[209].

### 9.3. H55

Farnesol is a sterol precursor that accumulates within cells in the event of an inhibition of sterol synthesis[210]. A cellular typing study revealed an antipyrene derivative, designated **H55**. This compound was shown to stimulate farnesol production through the suppression of the fungal enzyme C-24 sterol methyltransferase (ERG6)[211]. **H55** was found to act as a metastable Erg6 inhibitor, thereby effectively impeding the formation of the mycelium of *Candida albicans* and restoring virulent *Candida albicans* to a nonvirulent state in a mouse model of AZF-resistant candidiasis. In addition, **H55** has been shown to exhibit low toxicity to cells[210].

### 9.4. PQA-Az-13

PQA-Az-13 is a novel antifungal agent whose chemical structure incorporates imidazole, pyrrolidine, and aryl piperazine scaffolds, as well as a trifluoromethyl moiety[212]. This molecular configuration confers robust activity against multidrug-resistant *Candida auris*[212,213]. Experimental investigations revealed that PQA-Az-13 potently inhibits *C. auris* biofilms derived from ten distinct clinical isolates, with minimum inhibitory concentration (MIC) values ranging between 0.67 and 1.25 μg/mL. Proteomic studies further indicate that the compound suppresses the expression of several key enzymatic proteins in these biofilms, particularly those involved in amino acid biosynthesis, metabolic processes, and energy production[212]. Owing to its pronounced hydrophobicity and limited solubility in aqueous media, PQA-Az-13 was encapsulated in cationic liposomes formulated from soybean phosphatidylcholine (SPC), 1,2-dioleoyloxy-3-trimethylammonium-propane chloride (DOTAP), and DSPE-PEG 2000. This liposomal delivery system not only facilitates targeted administration but also enhances the compound's stability and mitigates its toxicity, as evidenced by its minimal adverse effects on normal human dermal fibroblasts. Moreover, PQA-Az-13 liposomes demonstrated superior antifungal efficacy in both *in vitro* biofilm assays and ex vivo skin colonization models[212].

Novel drugs or compounds targeting fungal hyphae and biofilms can exert multimodal antifungal effects by inhibiting the expression of hypha-specific genes (such as *ECE1*, *HWP1* and *UME6*), modulating sterol metabolism (for example, through Erg6), or disrupting biofilm metabolic pathways (for example, *via* amino acid synthases). These agents demonstrate low toxicity and high target specificity, for example, through the use of liposomal delivery systems for precise targeting, and hold promise for overcoming resistance. However, these methods still face limitations, including insufficient clinical translation data, uneven drug penetration due to the heterogeneous microenvironment of biofilms, and poor water solubility of some candidate compounds. Future improvement strategies should focus on developing broad-spectrum antibiofilm delivery systems (such as nanoparticles)[214], further elucidating the dynamic regulatory networks between hyphae and biofilms (for example, the interplay between farnesol signaling and morphological transitions)[215], and employing combination therapy strategies (such as coadministration with conventional azoles). In addition, potential new targets include core transcription factors involved in hyphal development (such as the downstream regulatory network of UME6)[216] and key molecules in the fungal quorum sensing system (for example, farnesol analogs)[217]. Research on these targets may offer novel avenues for antifungal therapy.

## 10. Antifungals targeting fungal intracellular metabolism

Intracellular metabolic pathways are essential for fungal proliferation and reproduction. The central metabolic network in fungi encompasses the glycolytic pathway, the tricarboxylic acid (TCA) cycle, and the fatty acid synthesis pathway[218]. The glycolytic route facilitates the conversion of glucose into energy, while the TCA cycle not only supplies additional energy but also furnishes critical intermediates under aerobic conditions. Concurrently, the fatty acid synthesis pathway is indispensable for constructing cellular membranes and storing energy[218,219]. Fungal metabolic pathways exhibit inherent complexity and redundancy, underscoring the adaptability of these organisms and revealing novel targets for antifungal drug development. Accordingly, therapeutic interventions designed to disrupt these pivotal metabolic routes can effectively suppress fungal proliferation and mitigate infection.

### 10.1. Olorofim

Dihydroorotate dehydrogenase (DHODH) plays an essential role in *de novo* pyrimidine biosynthesis. In this pathway, the enzyme catalyzes the oxidation of dihydroorotate to orotate, which constitutes the fourth step of pyrimidine synthesis[220,221]. Olorofim, a novel orotamine analog (Fig. 3), inhibits pyrimidine synthesis by targeting the dihydroorotic acid dehydrogenase of fungi, thereby disrupting fungal nucleic acid production and inhibiting mycelial elongation [220,222] (Fig. 1).

Olorofim has been shown to exhibit targeted inhibitory effects against a broad spectrum of pathogenic fungi, including *Aspergillus*, *Fusarium*, and saprophytic species such as *Scedosporium* spp.[13,223,224]. *In vitro* experiments have confirmed that Olorofim effectively kills *Aspergillus fumigatus* in a time-dependent fashion, causing mycelial lysis after approximately 34 h of exposure, followed by cell death at approximately 120 h. In several preclinical models, Olorofim has demonstrated

considerable potential against both invasive and endemic fungal infections. In a neutropenic mouse model of invasive pulmonary aspergillosis (IPA), the administration of Olorofim markedly improved survival outcomes[220,225]. A similar benefit was observed in a pulmonary aspergillosis model induced by *Aspergillus flavus*[226]. Furthermore, in murine models of central nervous system (CNS) coccidioidomycosis, treatment with Olorofim increased survival rates and progressively reduced the fungal burden in the brain[227]. In an immunosuppressed CD-1 mouse model-which was neutropenic *via* cyclophosphamide-intraperitoneal delivery of Olorofim not only extended survival but also significantly lowered $\beta$-D-glucan levels and the fungal DNA load[228]. Additionally, the compound has shown efficacy against endemic mycoses, including coccidioidomycosis and select foot and ankle infections[220,229]. Clinical data further indicate that Olorofim exhibits excellent tissue penetration, particularly in the lungs, liver, kidneys, and CNS (Table 2).

Olorofim is currently undergoing phase III clinical evaluation and has been granted regulatory designations by both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for its potential to treat a broad range of invasive fungal infections (ClinicalTrials.gov Identifier: NCT03583164)[224] (Fig. 4, Table 3).

### *10.2. T-2307*

T-2307 is an arylamine analog with structural similarity to other aromatic diamidines, such as pentamidine[230] (Fig. 3). Within fungal cells, the T-2307 compound selectively inhibits the respiratory chain complex within yeast mitochondria, resulting in a decrease in the mitochondrial membrane potential[231-233] (Fig. 1).

T-2307 is notably effective against clinically significant organisms, including *Candida albicans*, various *Pseudohyphomyces* species, *Cryptococcus neoformans*, and *Aspergillus fumigatus*[11,33,234]. In particular, it has shown significant antifungal effects on fluconazole-resistant and fluconazole-sensitive, dose-dependent *Candida albicans* strains[235,236], as well as azole-sensitive strains. In a variety of murine infection models (*e.g.*, *Candida* spp., *Cryptococcus* spp., and *Aspergillus fumigatus* infection models), T-2307 was shown to have a significant effect on mouse survival, demonstrating a dose-dependent effect and resulting in a substantial reduction in renal fungal load[233,237,238]. Importantly, T-2307 had a minimal effect on rat liver mitochondrial function, indicating its selective inhibitory effects on yeast mitochondria (Table 2). T-2307 is still in the early stages of clinical trials.

### *10.3. VL-2397*

VL-2397 is a cyclic hexapeptide compound that has been purified from the fermentation broth of *Acremonium persicinum*. It contains an iron carrier moiety with aluminum substituted for iron in its structure, which is unique among similar compounds (Fig. 3). VL-2397 is able to actively enter fungal cells through a fungus-specific membrane-bound transporter protein, iron-transferrin 1 (Sit 1), thereby triggering rapid and potent antifungal effects. However, since this transporter protein is not present in mammalian cells, VL-2397 does not enter human cells *via* this mechanism, resulting in high host selectivity[236,239-243].

In experimental settings, the *in vitro* efficacy of VL-2397 has been demonstrated to be significant against a diverse spectrum of fungal strains, which include azole-resistant variants of *Aspergillus* and other filamentous fungi that have evolved resistance to pharmaceutical agents, such as *Fusarium oxysporum*[34]. In a murine model of invasive aspergillosis (IA) induced by drug-resistant *Aspergillus* species, treatment with VL-2397 significantly improved survival rates while concurrently reducing the fungal burden in pulmonary tissues[34,239]. In addition, compared with many conventional antifungal medications, VL-2397 has been demonstrated to reduce off-target toxicity in the cytochrome P450-associated drug metabolism pathway. This finding suggests a diminished risk of concomitant drug interactions[244] (Table 2).

Although the compound has progressed to phase II clinical trials with the objective of evaluating its therapeutic potential, the decision was made in February 2019 to discontinue its development for reasons that have not been disclosed[244] (Fig. 4, Table 3).

### *10.4. Alkaloids of Waltheria spp.*

*Waltheria indica* is extensively employed in African traditional medicine for treating ailments such as diarrhea, cough, malaria, and skin infections, which are frequently associated with fungal pathogens such as *Candida* species[245]. Consequently, it is hypothesized that the leaves of this plant are rich sources of bioactive compounds with potential antifungal properties. Previous investigations have shown that alkaloids isolated from *W. indica* have significant inhibitory effects on a broad spectrum of fungi[246,247]. Experimental findings revealed that these alkaloids generate inhibition zones measuring 25 $\pm$ 0.10 mm against *Candida krusei* and 23 $\pm$ 0.25 mm against *Candida tropicalis*, with corresponding minimum inhibitory concentrations (MICs) of 0.50 and 0.75 mg/mL and minimum fungicidal concentrations (MFCs) of 0.75 and 1.25 mg/mL, respectively. These data underscore the efficacy of alkaloids in suppressing fungal growth, with particularly robust activity against *C. krusei*. Moreover, it is postulated that their antifungal mechanism involves disruption of fungal cell membranes and interference with cellular energy metabolism[245].

### *10.5. Compounds YU253467 and YU254403*

Phosphatidylserine decarboxylase (PSD) is essential for cellular metabolism and significantly contributes to fungal pathogenicity, making it a promising target for antifungal drug development. In a recent high-throughput screening study, two promising compounds, YU253467 and YU254403, were identified. These agents exhibited potent antifungal activity against *Candida albicans* and *Aspergillus fumigatus*, along with moderate efficacy against *Candida smoothii*. However, this inhibitory effect was significantly diminished in the presence of ethanolamine, indicating that the antifungal mechanism may be associated with the inhibition of the mitochondrial activity of phosphatidylserine decarboxylase[248].

Novel antifungal agents that target fungal cell metabolism exhibit broad-spectrum activity by disrupting key metabolic pathways while also demonstrating high host selectivity and the potential for overcoming resistance. These agents act by inhibiting pyrimidine synthesis, impairing mitochondrial function, and modulating iron metabolism, among other mechanisms. However, given the complexity and redundancy of fungal metabolic networks, the inhibition of a single target may be compensated for; consequently, some compounds have been discontinued during development owing to unclear mechanisms (for example, VL-2397), and the long-term safety of mitochondrial-targeting agents (such as T-2307) remains to be fully validated. In addition to the pathways mentioned above, potential targets include enzymes

involved in lipid metabolism (such as phosphatidylserine decarboxylase)[249], key enzymes involved in amino acid biosynthesis (such as phosphoglycerate dehydrogenase (PHGDH))[250], and core components of the redox system (such as thioredoxin reductase)[251]. Fungal $F_1F_o$ ATP synthase plays a central role in fungal energy metabolism and pathogenicity[252], and *ATP16* deletion mutants in fungal cells exhibit downregulated virulence factors and reduced pathogenicity. The identification of a compound potentially targeting the $\delta$ subunit of the fungal $F_1F_o$-ATP synthase induced an *in vitro* phenotype similar to that observed in the *ATP16* deletion mutant and protected mice from death from invasive candidiasis[253]. Thus, $F_1F_o$-ATP synthase is also a potential target for antifungal therapy. Moreover, fungal-specific two-component signaling systems-exemplified by the Hog1−MAPK pathway-which regulates osmotic pressure and drug tolerance, may be exploited to increase drug sensitivity through the inhibition of their histidine kinases or response regulators[254]. Strategies targeting enzymes involved in fungal toxin synthesis (such as polyketide synthases)[255], cell cycle-dependent kinases (CDKs)[256], or spindle assembly checkpoint proteins[256] also offer promising avenues for inhibiting fungal proliferation.

## 11. Dual-targeted antifungal agents

The study of dual-targeted antifungal drugs is currently emerging as an important innovative strategy designed to increase therapeutic efficacy and reduce the risk of drug resistance by acting simultaneously on multiple key fungal targets[257]. These targets encompass a range of essential fungal processes, including cell membrane structure and function, DNA synthesis and repair, core metabolic pathways, mitochondrial function, and fungal response mechanisms to external stresses[258]. By interfering with these key processes, dual-targeted drugs are able to achieve a synergistic effect, resulting in greater antifungal activity at lower doses. Furthermore, these drugs typically demonstrate broad-spectrum antifungal activity and are capable of inhibiting multiple drug-resistant fungal strains while exhibiting high selectivity and good biocompatibility with reduced toxicity to host cells. The multi-target intervention mode of dual-targeted drugs offers a novel approach to address the issue of antifungal drug resistance, with the potential to advance the field of antifungal therapy in the future.

### 11.1. $(Gly_{0.8}Nap_{0.2})_{20}$

The compound $(Gly_{0.8}Nap_{0.2})_{20}$ is designed on the basis of natural host defense peptides (HDPs), which utilize poly(2-oxazoline)s as the fundamental backbone while incorporating naphthyl (Nap) groups as hydrophobic units to mimic the hydrophobic domains of HDPs. Through this biomimetic amphiphilic structure, combined with the controlled polymerization of poly(2-oxazoline)s and the hydrophobic/DNA-targeting functionality of the naphthyl groups, $(Gly_{0.8}Nap_{0.2})_{20}$ has emerged as a novel polypeptide-based antifungal compound[257].

*In vitro*, assays have confirmed that $(Gly_{0.8}Nap_{0.2})_{20}$ exhibits robust antifungal activity against several drug-resistant fungal pathogens of clinical importance, including *Candida albicans* and *Aspergillus fumigatus*. The minimum inhibitory concentrations of the compounds ranged from 0.78 to 3.13 μg/mL, a potency comparable to that of amphotericin B, which has MIC values between 0.78 and 1.56 μg/mL. Moreover, $(Gly_{0.8}Nap_{0.2})_{20}$ demonstrated superior selectivity toward red blood cells and fibroblasts ($HC_{50}$/MIC = 1−2, $IC_{50}$/MIC = 1−2) compared with amphotericin B, indicating both excellent antifungal activity and enhanced biosafety. In antifungal resistance risk assessment experiments, researchers reported that after 30 consecutive passages of *C. albicans* and its fluconazole-resistant strains were treated with $(Gly_{0.8}Nap_{0.2})_{20}$ and fluconazole, the MIC of $(Gly_{0.8}Nap_{0.2})_{20}$ remained stable, whereas fluconazole resistance increased by more than 6400-fold. In animal models, $(Gly_{0.8}Nap_{0.2})_{20}$ exhibited therapeutic efficacy comparable to that of clinically approved antifungal drugs in mouse models of keratitis and skin abrasion infections. It significantly reduced the fungal burden at the infection site, mitigated hyphal invasion, and caused no apparent toxicity. In a systemic *C. albicans* infection model, the compound effectively improved survival rates in infected mice, comparable to amphotericin B, and successfully eradicated fungal loads from multiple organs, including the heart and kidneys, preventing further fungal invasion of critical organs. Histological analysis and blood biochemical indicators further confirmed the excellent *in vivo* biocompatibility and safety of $(Gly_{0.8}Nap_{0.2})_{20}$, supporting its potential application in treating systemic infections caused by drug-resistant fungi[257]. In summary, $(Gly_{0.8}Nap_{0.2})_{20}$ offers a promising strategy for addressing antifungal resistance through its innovative dual-targeting mechanism, potent antifungal activity, and favorable biosafety profile[257].

### 11.2. CYP51/HSP90-related dual-target inhibitors

Current reports on dual-target antifungal agents encompass several categories. Notable classes include inhibitors that simultaneously target ergosterol 14$\alpha$-demethylase (CYP51) and histone deacetylase (HDAC)[259]; compounds that inhibit both heat shock protein 90 (HSP90)[260] and HDAC; and molecules that act on squalene epoxidase (SE) and CYP51[261].

On the basis of the fusion of key pharmacophores from CYP51 inhibitors (triazole derivatives) and HDAC inhibitors (featuring zinc-binding hydroxamic acid moieties), dual CYP51/HDAC inhibitors have been developed as multitarget antifungal agents. These compounds primarily exert broad-spectrum antifungal activity by synergistically inhibiting fungal sterol biosynthesis and modulating epigenetic regulation. Recent experimental investigations have confirmed that the novel agent **A5** exhibits robust *in vitro* antifungal efficacy against fluconazole-resistant strains of *Candida tropicalis* and *Cryptococcus neoformans*, achieving $MIC_{80}$ values of 0.5 μg/mL for both organisms. These potency levels are markedly superior to those of fluconazole and the HDAC inhibitor SAHA, which both have $MIC_{80}$ values exceeding 64 μg/mL in resistant isolates. Mechanistic investigations revealed that A5 acts *via* a dual mechanism-first, by inhibiting CYP51 activity, thereby disrupting ergosterol biosynthesis and leading to a 2.4- to 4.5-fold downregulation of *ERG1* and *ERG11* gene expression; second, by inhibiting HDAC activity, which results in a 3.8-fold increase in histone H3 acetylation and subsequent downregulation of virulence-associated genes. Notably, A5 completely abrogates the filamentation of *Candida tropicalis* at 1 μg/mL and achieves 100% inhibition of biofilm formation at 64 μg/mL, while reducing the capsule thickness of *Cryptococcus neoformans* by 58% ($P < 0.0001$), an effect closely correlated with a 3.2- to 5.7-fold downregulation of *CAP10*/*CAP60* gene expression. *In vivo*, A5 prolonged the median survival of *Cryptococcus neoformans*-infected mice from 6 to 11 days (83% increase) and exhibited low cytotoxicity (HUVEC

$IC_{50}$ = 5.9 μg/mL, approximately 12-fold greater than its active antifungal concentration)[259].

Dual inhibitors targeting HSP90 and HDAC have been developed by integrating the pharmacophoric elements of ganetespib, a potent HSP90 inhibitor, with those of HDAC inhibitors such as SAHA. Preclinical studies have demonstrated that these agents possess substantial antifungal activity against azole-resistant *Candida albicans*. Notably, among the synthesized derivatives, compound **J5** exhibited robust synergistic effects, as reflected by a FICI value of 0.266 *in vitro*, confirming its efficacy *in vivo*. **J5** selectively targets fungal HSP90 and HDAC enzymes, contributing to reduced toxicity. Mechanistic investigations revealed that **J5** enhances the antifungal potency of fluconazole by suppressing key virulence traits-including biofilm formation and hyphal development, by downregulating resistance-associated genes such as *ERG11* and *CDR1*. Furthermore, *in vivo* experiments demonstrated that treatment with **J5** significantly decreased renal fungal burdens in infected mice ($P < 0.001$), underscoring its potential as a clinical candidate for managing azole-resistant candidiasis[260].

Dual inhibitors targeting CYP51 and squalene epoxidase (SE) are a series of compounds developed *via* pharmacophore models derived from established SE and CYP51 inhibitors. Preliminary mechanistic studies revealed that compound **8** simultaneously impedes the functions of SE and CYP51 in *Candida albicans*, thereby disrupting ergosterol biosynthesis and ultimately inducing fungal cell death. The experimental data indicate that compound **8** achieves a minimum inhibitory concentration (MIC) of 3 mg/L, underscoring its considerable antifungal efficacy. Moreover, molecular docking analyses have validated the binding interactions of compound **8** with the active sites of both SE and CYP51, providing a solid theoretical basis for its further optimization and the advancement of novel antifungal agents[261].

Furthermore, a recent study reported a novel dual inhibitor, ketaminazole, which simultaneously targets fungal CYP51 and human 5-lipoxygenase (5-LOX), demonstrating significant antifungal potential. Experimental data indicate that ketaminazole has an $IC_{50}$ of 43 nmol/L against CYP51 and shows a 17-fold greater inhibitory selectivity for yeast CYP51 than its human counterpart selectivity that surpasses that of the current antifungal agent ketoconazole. In addition, whole blood assays revealed that ketaminazole effectively reduces leukotriene B4 (LTB4) synthesis, achieving an inhibition rate of 45% at a concentration of 10 μmol/L. These findings suggest that ketaminazole not only possesses potent antifungal activity but also has anti-inflammatory effects[262].

On the basis of a CYP51/HSP90-related dual-target mechanism, these antifungal compounds exhibit significant advantages by synergistically interfering with key fungal survival pathways, such as ergosterol biosynthesis and epigenetic regulation. However, these compounds still face challenges, including structural complexity (which requires a balance between the triazole ring and the zinc-binding group), potential toxicity risks (as HDAC inhibition might interfere with host epigenetic regulation), and pharmacokinetic issues. To increase both safety and efficacy, computational modeling is recommended to optimize the spatial configuration of the pharmacophores for improved target selectivity, to develop subtype-specific HDAC inhibitors to reduce off-target effects, and to systematically assess their metabolic stability (*e.g.*, *via* hepatic enzyme pathways) and long-term toxicity (with particular attention to epigenetic-related side effects).

## 12. Antifungal agents that act on host immunity

In addition to conventional antifungal agents, adjuvant immunotherapy has emerged as a promising strategy for the management of drug-resistant fungal infections. Compared with standard antifungal drugs, immunotherapy offers a superior safety profile and a reduced likelihood of resistance development, thereby exhibiting considerable clinical potential. Preclinical studies and clinical trials have demonstrated that combining conventional antifungal therapy with adjuvant immunotherapy significantly enhances therapeutic efficacy and improves patient outcomes[263]. Current approaches in adjuvant immunotherapy include the use of antimicrobial peptides with intrinsic antifungal properties, the coadministration of immune-activating cytokines alongside antifungal agents, and both prophylactic and therapeutic applications of antifungal antibodies and vaccines.

### 12.1. Antifungal peptides

Antifungal peptides constitute a diverse class of bioactive molecules widely distributed across plants, animals, and microorganisms, where they function as pivotal components of the innate immune defense against pathogenic invasions[264,265]. These agents are primarily short-chain, cationic peptides characterized by structural heterogeneity and multiple mechanisms of action[266]. Naturally occurring antifungal peptides include $\beta$-defensins, histones, LL-37, and filamentous proteins, among others[267,268]. They exert antifungal activity predominantly by compromising the integrity of fungal cell membranes and triggering the efflux of intracellular contents[269]. Owing to their broad-spectrum antimicrobial properties, favorable safety profiles, and reduced propensity to induce resistance, antifungal peptides have emerged as promising candidates for drug discovery and development. Notably, several peptide-based antifungal agents are currently progressing through clinical trials, underscoring their significant therapeutic potential (Table 4[268,270-276,278-313]).

#### 12.1.1. NP213

NP213 is a water-soluble cyclic antimicrobial peptide developed from a host defense peptide (HDP) template and optimized for the topical treatment of onychomycosis[314]. NP213, which is composed of a cyclized homopolymer of seven L-arginine residues and possesses a net positive charge of +7, is structurally tailored to penetrate skin and nail tissues efficiently[315]. Preclinical and clinical assessments have consistently demonstrated excellent safety and tolerability, with data showing no evidence of a placebo effect. *In vitro* evaluations revealed that NP213 rapidly exerts bactericidal effects in aqueous formulations and effectively eradicates multiple strains of *Trichophyton rubrum*, even in the presence of human nails and keratin, thereby outperforming existing antifungal agents[314]. Furthermore, two-phase IIa clinical trials have substantiated its therapeutic potential; one study reported that 43.3% of patients exhibited no detectable fungi in nail fragments after 180 days of treatment, whereas another trial reported that 56.5% of patients had negative dermatophyte cultures following 360 days of therapy[314] (Table 4).

**Table 4** The mechanism of action of immunomodulatory antifungal drugs and the latest clinical trial results.

| Therapy type | Agent name | Target indication | Target pathogen | Development stage | ClinicalTrials.gov ID | Ref. |
|---|---|---|---|---|---|---|
| Antifungal peptides | HXP124 | Onychomycosis | *Candida* spp., *Cryptococcus* spp., dermatophytes and non-dermatophyte molds | Phase I/IIa | ACTRN12618000131257 | 268 |
| | NP213 (Novexatin) | Onychomycosis | *Trichophyton rubrum*, Dermatophytes | Phase I/IIa, IIa | 2008-001496-29, NCT02343627, NCT02933879 | 270 |
| | hLF1-11 | Prophylaxis in HSCT patients | *Candida* spp. | Phase II | NCT00509938, NCT00430469, NCT00509834 | 271 |
| | P113 | Oral candidiasis | *Candida* spp. | Phase I/IIa, IIb | NCT00659971 | 268,272-274 |
| | CZEN-002 | VVC | *Candida* spp. | Phase I/IIa | – | 268 |
| | Pexiganan (MSI-78) | Diabetic foot ulcer infection | Gram-positive, gram-negative, anaerobic bacteria, fungi and parasites | Phase III | NCT00563394, NCT00563433 | 275 |
| | Omiganan (MX-226 or MBI-226) | Dermal infection | *Candida* spp. | Phase II, III | NCT02849262, NCT02596074, NCT00027248, NCT00231153, 2015-002724-16, 2015-005553-13 | 276 |
| | Iseganan (IB-367) | Oral mucositis, ventilator-associated pneumonia | *Candida* spp. | Phase III | NCT00118781 | – |
| | LTX-109 | No special | *Staphylococcus aureus*, *Saccharomyces cerevisiae* | Phase I/IIa | NCT01158235, NCT01803035, NCT01223222 | 278 |
| Cytokine therapy | IFNγ | Trichomoniasis, candidiasis, CGD, AIDS patients, leukemia, transplant patients, cryptococcal meningitis, | *Aspergillus* spp., *Candida* spp., *Cryptococcus*, *Staphylococcus aureus* | FDA approved | NCT05235711, NCT00059878, NCT01270490, NCT01147042, NCT04979052, NCT00012467, NCT05653193, NCT00814827 | 279–289 |
| | G-CSF | Invasive candidiasis, cancer chemotherapy patients, prophylaxis in HSCT patients, trichotillomania | – | Clinical | NCT02933333 | 290–292 |
| | GM-CSF | Prophylaxis in HSCT patients, AIDS patients, acute myeloid leukemia patients, trichotillomania, candidiasis | – | FDA approved | NCT06472739, NCT02933333, NCT01232504 | 293–297 |
| | M-CSF | Prophylaxis in HSCT patients | *Candida* spp. | Phase I | – | 298 |
| Immune checkpoint inhibitors | Nivolumab | Mucormycosis | Mucorales | Case study (1 patient) | – | – |
| Vaccines | NDV-3A | VVC | *Candida* spp. | Phase Ib/IIa | NCT01926028, | 299 |

(*continued on next page*)

**Table 4** (*continued*)

| Therapy type | Agent name | Target indication | Target pathogen | Development stage | ClinicalTrials.gov ID | Ref. |
|---|---|---|---|---|---|---|
| | | | | | NCT02996448, NCT03455309 | |
| | PEV7 | VVC | *Candida* spp. | Phase I | NCT01067131 | 300 |
| | D.651 | VVC | *Candida* spp. | Phase II | – | 301 |
| | Killed *Coccidioides immitis* spherule Vaccine | Coccidioidomycosis | Coccidioidomycetes | Phase III | – | 302 |
| Monoclonal antibodies | 18B7 | Cryptococcosis | *Cryptococcus neoformans* | Phase I | – | 303 |
| | Efungumab (Mycograb) | Candidiasis | C. Albicans | Clinical | NCT00324025, NCT00847678 | 304 |
| Cellular therapy | CAR-T | Invasive aspergillosis | *Aspergillus fumigatus, Cryptococcus neoformans* | *In vivo* (murine) | – | 305–307 |
| | Granulocyte transfusion | Neutropenia, prophylaxis in HSCT patients | – | Clinical | – | 308,309 |
| | Adaptive T-cell transfusion | Diffuse invasive aspergillosis, invasive aspergillosis, prophylaxis in HSCT patients | – | Clinical | – | 310–312 |
| Other immunotherapies | Ruxolitinib | Patients with GOF mutations in STAT1 or STAT3, CMC | – | Clinical | – | 313 |

The results of the latest clinical trials from https://clinicaltrials.gov/ (March 2025).

#### *12.1.2. hLF1-11*

The human lactoferrin-derived peptide hLF1-11, comprising the initial 11 amino acids from the protein's N-terminal region, represents a novel antimicrobial agent. This peptide exhibits a broad spectrum of activity, including antibacterial, antifungal, and immunomodulatory properties[268]. Its therapeutic potential has been principally evaluated in the context of infectious diseases, particularly those caused by drug-resistant bacteria and fungi. Both preclinical and clinical studies indicate that hLF1-11 is well tolerated and has a favorable safety profile[316,317]. *In vitro* experiments revealed that hLF1-11 effectively inhibits *Candida albicans* by preventing biofilm formation and suppressing its metabolic activity. Moreover, when used in combination with established antifungal drugs such as fluconazole and caspofungin, hLF1-11 exhibits synergistic effects that increase their antimicrobial efficacy[318,319]. A preliminary clinical trial involving 48 healthy volunteers (36 receiving hLF1-11 and 12 receiving placebo) as well as 8 autologous hematopoietic stem cell transplant patients confirmed that the peptide is well tolerated, with no significant adverse effects observed[271] (Table 4).

#### *12.1.3. HXP124*

HXP124, a peptide isolated from plant sources, has potent antifungal efficacy against a wide range of fungal pathogens. Its activity extends to clinically relevant organisms, including species of *Candida* and *Cryptococcus*, as well as dermatophytes and non-dermatophyte molds[268]. In the context of onychomycosis treatment, HXP124 has notable potential because it effectively penetrates the nail plate and inhibits the causative fungi[268]. Clinical evaluations have confirmed its favorable safety and tolerability profile alongside significant therapeutic efficacy in nail fungal infections. For example, in a phase I/IIa trial involving 41 patients with mild to moderate toenail onychomycosis, daily topical application of HXP124 for 6 weeks resulted in a reduction in the infected area by more than 40% in 37% of participants, compared with 18% in the control group (https://hexima.com.au/) (Table 4).

#### *12.1.4. P113*

P113 is a synthetic antimicrobial peptide derived from human histone H1 that exhibits broad-spectrum antibacterial and antifungal activities. In addition to containing 12 amino acid residues (sequence: AKRHHGYKRKFH), it was developed primarily for the management of localized oral Candida infections, such as oral candidiasis[320]. The antimicrobial activity of the peptide is attributed primarily to its ability to disrupt microbial cell membranes. Its positively charged amino acid residues interact with membrane phospholipids, inducing the formation of transmembrane pores that facilitate the efflux of intracellular contents and ultimately result in cell death[320]. Clinical studies have confirmed that P113, when applied as an oral mouthwash, is both safe and well tolerated, effectively preventing and treating oral infections of fungal and bacterial origin. In a phase I/IIa clinical trial, 37% of patients achieved a clinical cure after 14 days of treatment with P113[268]. Furthermore, several double-blind, randomized controlled studies have corroborated its favorable safety profile, and treatment with Nal-P113 has been shown to significantly enhance periodontal outcomes while reducing plaque accumulation and biofilm formation compared with those of controls[272-274] (Table 4).

#### *12.1.5. CZEN-002*

CZEN-002, also known as CKPV2, is a novel antifungal peptide engineered by Abiogen Pharma SpA and is derived from alpha-

melanocyte-stimulating hormone ($\alpha$-MSH) for the treatment of vulvovaginal candidiasis[321]. This agent displays extensive antimicrobial efficacy, targeting a spectrum of pathogens, including *Candida albicans*, *Candida krusei*, and *Candida glabrata*, as well as both gram-positive and gram-negative bacteria[322]. Additionally, CZEN-002 modulates the host immune response by reducing macrophage-mediated phagocytosis of *Candida albicans* and suppressing the production of proinflammatory cytokines-namely, TNF-$\alpha$, IL-1$\beta$, and IL-6-while increasing the secretion of the anti-inflammatory cytokine IL-10[321]. In phase I/IIa clinical trial involving 18 female patients, treatment with CZEN-002 achieved cure rates of 88.2% and 87.5%, as determined by KOH examination and culture, respectively[268] (Table 4).

#### *12.1.6. Pexiganan (MSI-78)*

Developed as a synthetic analog of magainin 2, pexiganan (MSI-78) is derived from an antimicrobial peptide originally isolated from the skin of the African clawed toad[323]. Compared with 22 amino acids, this peptide exerts broad-spectrum antimicrobial effects by compromising the integrity of microbial cell membranes. Its mechanism of action is effective against a wide range of pathogens, including Gram-positive and Gram-negative bacteria, anaerobes, fungi, and parasites[324]. Clinical investigations have highlighted its potential, particularly in managing infections associated with diabetic foot ulcers[275]. Both *in vitro* and *in vivo* studies have demonstrated that pexiganan significantly reduces bacterial loads at infection sites, and clinical trials have confirmed its favorable safety profile with minimal adverse effects[325]. Moreover, two successive phase III double-blind controlled trials reported that topical pexiganan achieved clinical improvement in 85%−90% of patients, microbial eradication in 42%−47% of patients, and wound healing outcomes comparable to those observed with oral ofloxacin, all without evidence of resistance development[275] (Table 4).

## 13. Immune cytokines

Cytokines are low-molecular-weight proteins secreted by both immune and nonimmune cells that play essential roles in regulating host defense and mediating inflammatory processes. Within antifungal immunity, pivotal cytokines-including interferon-gamma (IFN-$\gamma$), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-12 (IL-12), and interleukin-17 (IL-17)-serve as key regulators of both innate and adaptive immune responses[326]. *In vitro* investigations have demonstrated that treatment with these cytokines enhances the resistance of the host to fungal pathogens.

### *13.1. IFN-$\gamma$*

Interferon-$\gamma$ (IFN-$\gamma$) is a cytokine that is predominantly secreted by activated T lymphocytes and natural killer cells and plays multifaceted roles in antifungal immunity[327]. It enhances the phagocytic and fungicidal activities of macrophages and neutrophils, thereby facilitating the clearance of fungal pathogens[328]. Moreover, IFN-$\gamma$ augments the antigen-presenting capacity of phagocytes, which in turn potentiates adaptive immune responses[328]. Clinical studies have shown that adjunctive administration of recombinant IFN-$\gamma$ combined with antifungal agents markedly decreases the occurrence of invasive fungal and bacterial infections in immunocompromised patients, including those with HIV, organ or bone marrow transplant recipients, chemotherapy patients, and individuals with chronic granulomatous disease[268]. This integrated treatment approach has been demonstrated to reduce infections caused by pathogens such as *Candida* spp.[280,329], *Aspergillus* spp.[280,330,331], *Cryptococcus* spp.[329], *Staphylococcus aureus*, and other bacteria[329]. Moreover, IFN-$\gamma$ has been granted FDA approval for the management of chronic granulomatous disease in patients at high risk for invasive fungal and opportunistic infections[279,332] (Table 4).

### *13.2. G-CSF*

Granulocyte colony-stimulating factor (G-CSF) is a critical regulator of neutrophil production and function[333]. Deficiencies in G-CSF or its receptor result in a significant reduction in neutrophil counts[333-335]. Multiple investigations have revealed a clear association between fungal infection risk and the duration and severity of neutropenia. Consequently, adjunctive treatment combining G-CSF with conventional antifungal agents is routinely employed to improve clinical outcomes in affected patients[336,337]. For example, Grigull et al.[290] reported that three pediatric patients with fungal infections associated with hematologic malignancies achieved effective infection control following a regimen of G-CSF and antifungal drugs. Similarly, a pediatric patient with Card9 deficiency and invasive Candida infection involving the abdominal cavity and central nervous system exhibited marked clinical improvement after receiving combination therapy with G-CSF and antifungal agents[291]. Moreover, B. Sahin et al.[292] reported that 4 patients with *Trichophyton mentagrophytes* infections treated with high-dose G-CSF alongside either fluconazole or amphotericin B not only survived but also showed significant increases in neutrophil counts (Table 4).

### *13.3. GM-CSF*

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine that modulates a wide range of myeloid cells[333]. It has been shown to increase neutrophil production of reactive oxygen species (ROS) in response to fungal challenges, thereby promoting the clearance of fungal pathogens by the immune system[338,339]. Recent investigations revealed that GM-CSF secreted by epithelial immune cells facilitates the recruitment of responsive neutrophils and improves their fungicidal function[340]. Clinically, GM-CSF is approved for managing chemotherapy-induced neutropenia and is routinely integrated into hematopoietic stem cell transplantation protocols[293]. For example, in a phase IV clinical trial involving patients undergoing allogeneic hematopoietic stem cell transplantation, GM-CSF administration was associated with a reduction in morbidity and mortality attributable to invasive candidiasis[294]. Moreover, neutropenic patients with bacterial or fungal infections receiving combined therapy with GM-CSF and antifungal agents experienced significantly higher survival rates than those treated solely with antifungal medications[295]. Additionally, GM-CSF has been used as adjunctive therapy in HIV-infected individuals with fungal infections and in patients with refractory invasive fungal diseases[296,297] (Table 4).

### *13.4. M-CSF*

Macrophage colony-stimulating factor (M-CSF) is essential for the expansion, maturation, and functional activation of monocytes and macrophages. In addition to its role in hematopoiesis, M-CSF

serves as a vital immunomodulator in controlling fungal infections, particularly those that are drug-resistant or recalcitrant[298]. For example, in a rat model of acute candidiasis, the combined use of M-CSF with fluconazole resulted in a synergistic improvement in survival outcomes[341]. Similarly, in a murine model of cryptococcosis, M-CSF monotherapy significantly reduced the fungal burden[342]. Moreover, among bone marrow transplant recipients with *Candida* infections, patients treated with recombinant human M-CSF (rhM-CSF) exhibited increased survival compared with those who did not receive rhM-CSF[298] (Table 4).

## 14. Vaccine

Vaccines are biologically active formulations that stimulate the host immune system to generate targeted responses, thereby conferring protection against specific pathogens. Similarly, fungal vaccines have demonstrated efficacy in preventing infections by priming both humoral and cellular immune mechanisms. This vaccination strategy establishes a robust protective barrier that reduces the risk of fungal invasion upon re-exposure[343].

### *14.1. NDV-3*

NDV-3 is an investigational vaccine derived from a recombinant N-terminal segment of the Als3 protein of *Candida albicans* that was developed to prevent recurrent vulvovaginal candidiasis (VVC)[344]. The Als3 protein serves as a mycelium-specific virulence factor that facilitates adhesion to and invasion of human epithelial and vascular endothelial cells by *C. albicans*[345]. Preclinical studies have shown that mice immunized with NDV-3 develop significantly elevated serum antibody levels against Als3, and in a murine model of *C. albicans* infection, vaccination increased survival by 60% relative to that of unvaccinated controls[346]. Furthermore, a phase Ib/IIa clinical trial involving 188 female patients with recurrent VVC demonstrated that NDV-3 is both safe and highly immunogenic; notably, vaccinated women under 40 years of age experienced a marked reduction in the frequency of symptomatic episodes over a 12-month follow-up period[299] (Table 4).

### *14.2. PEV7*

PEV7 is an antifungal vaccine candidate developed by Pevion Biotech AG for the prevention of *Candida vaginitis*[300]. It comprises a truncated recombinant variant of *Candida albicans*-secreted aspartyl protease 2 (Sap2) encapsulated within influenza virosomes. Sap2 serves as a critical virulence factor and immunogen in mucosal infections caused by *C. albicans*. By incorporating Sap2 into the virosome, the vaccine formulation effectively enhances immunogenicity and activates the host immune response[300]. Preclinical and clinical investigations have demonstrated a favorable safety and efficacy profile for PEV7. In a rat model of Candida vaginitis, immunization with PEV7 elicited robust local production of anti-Sap2 IgG and IgA antibodies, which accelerated the clearance of the fungus from the vaginal mucosa and exhibited significant therapeutic efficacy[300,347]. Furthermore, a phase I clinical trial involving 48 healthy female volunteers confirmed that PEV7 is both safe and highly immunogenic[300] (Table 4).

### *14.3. D.651*

D.651 is an oral vaccine formulated using ribosomes derived from *Candida albicans* serotypes A and B combined with a membrane proteoglycan isolated from *Klebsiella pneumoniae* lacking an envelope that is intended for the prevention of recurrent vulvovaginal candidiasis (VVC)[301]. In a phase II open-label trial, D.651 demonstrated favorable safety and efficacy profiles. Among 20 patients with recurrent VVC, 13 experienced no recurrence within 6 months following vaccination[301]. Notably, prior to immunization, these patients averaged 3.59 VVC episodes over 6 months, a rate that decreased to an average of 0.55 episodes per 6 months post-vaccination[301] (Table 4).

### *14.4. Killed Coccidioides immitis spherule vaccine*

The killed *Coccidioides immitis* Spherule Vaccine is formulated from formaldehyde-inactivated spherules of *Coccidioides immitis*[302]. In preclinical animal models, vaccination with this preparation effectively prevented fatal coccidioidomycosis. However, a phase III clinical trial involving 2867 healthy volunteers revealed only a marginal, statistically insignificant reduction in coccidioidomycosis incidence in the vaccinated cohort compared with the placebo group; additionally, the vaccine elicited both local and systemic adverse reactions, leading to the suspension of its development[302].

In parallel, several novel vaccine platforms-such as epitope peptide-based vaccines and virus-like particle (VLP) vaccines-have demonstrated promising preclinical efficacy. For example, the NXT-2 vaccine, a panfungal candidate developed from conserved homologous sequences of multiple fungal pathogens (*e.g.*, *Pneumocystis carinii*, *Aspergillus*, *Candida*, and *Cryptococcus* spp.), has shown robust immunogenicity and protective efficacy in murine models of invasive aspergillosis, candidiasis, and Pneumocystis pneumonia[348]. Moreover, Singh et al.[349] reported that immunization with antigenic formulations comprising both the Als3 and Hyr1 proteins, administered with either complete Freund's adjuvant (CFA) or incomplete Freund's adjuvant (IFA), elicited strong antibody responses, thereby protecting neonatal mice against candidiasis. Finally, the breakthroughs achieved with mRNA vaccine technology during the COVID-19 pandemic have opened new avenues for fungal vaccine development, offering innovative strategies to increase immunogenicity and protective efficacy[350-352] (Table 4).

## 15. Antibodies

Monoclonal antibodies (MAbs) have made tremendous progress in the treatment of tumors, autoimmune diseases, infectious diseases, etc. Monoclonal antibodies eliminate pathogens or target cells through direct blockade, as well as by mediating antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC)[351]. Given the limitations of conventional antifungal agents in addressing highly drug-resistant fungal infections, current research is increasingly focused on developing MAb-based therapies for the treatment of severe fungal diseases.

### *15.1. ch18B7*

ch18B7 is a chimeric monoclonal antibody engineered by fusing the variable domain of the murine IgG1$\kappa$ monoclonal antibody 18B7 with the constant region of human IgG1$\kappa$[303]. It specifically binds to glucuronoxylomannan (GXM), the primary polysaccharide constituent of the *Cryptococcus neoformans* capsule and a key virulence determinant[303]. Preclinical evaluations have

demonstrated that ch18B7 has a favorable efficacy and safety profile, indicating that it is effective in both the prevention and treatment of *C. neoformans* infections. In murine models, ch18B7 administration accelerated the clearance of fungal antigens, reduced fungal burden, and significantly improved survival outcomes[353]. Moreover, when combined with antifungal agents, ch18B7 displays synergistic interactions that further augment its therapeutic benefits[303]. In a Phase I clinical trial, administration of 18B7 to patients with cryptococcal meningitis, following antifungal therapy, was well tolerated and resulted in decreased levels of *de novo* cryptococcal antigens[354] (Table 4).

### *15.2. Efungumab (Mycograb)*

Efungumab is a recombinant human monoclonal antibody engineered to selectively bind fungal heat shock protein 90 (HSP90), thereby compromising fungal viability[355]. It has broad-spectrum antifungal activity against multiple *Candida* species, including *C. albicans* and *C. tropicalis*. *In vitro* experiments have shown that Efungumab synergizes with antifungal agents such as fluconazole, amphotericin B, and caspofungin[355]. In a murine model of systemic candidiasis, a one-time 2 mg/kg dose of Efungumab combined with amphotericin B markedly decreased average organ colony counts and reduced the incidence of positive biopsy specimens[355]. Additionally, a clinical study in adult patients with invasive candidiasis revealed that combining Efungumab with a lipid-based amphotericin B formulation enhanced therapeutic efficacy relative to the lipid formulation alone, lowering mortality from 18% to 4%[304].

Despite these promising findings, further clinical development of Efungumab and similar antibodies has not been pursued for various reasons. Nevertheless, numerous newly developed antifungal antibodies have demonstrated encouraging preclinical results. For example, H5K1-a humanized monoclonal antibody targeting $\beta$-1,3-glucan-significantly inhibited *Candida* growth *in vitro* and exhibited enhanced antifungal effects when combined with caspofungin and amphotericin B[356,357]. Additionally, Antonio Cassone and colleagues reported two monospecific human single-domain antibodies (DAbs) directed against mannoprotein MP65 and *Candida albicans* secretory aspartyl protease (Sap2), both of which accelerated the clearance of vaginal fungal infections in rat models[358] (Table 4).

## 16. Other immunotherapies

Recent investigations have demonstrated that increased expression of immune checkpoint molecules, including programmed death-1 (PD-1), lymphocyte-activation gene 3 (LAG-3), and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), is associated with impaired antifungal immunity[351]. Elevated levels of these markers have been detected in the peripheral blood of patients with invasive candidiasis. Treatment with PD-1/PDL-1 or CTLA-4 antibodies significantly improves survival in a variety of fungal models, including the *Histoplasma capsulatum* mouse model, the *Candida albicans* sepsis mouse model, and the mouse model of cryptococcosis[359-361]. Moreover, elevated levels of these markers have been detected in the peripheral blood of patients with invasive candidiasis[268]. In a clinical case involving an invasive fungal infection refractory to conventional antifungal therapy, the patient's condition markedly improved following combination treatment with the PD-1-blocking antibody nab-palivizumab, interferon-gamma (IFN-$\gamma$), and antifungal agents (amphotericin B and posaconazole) [362].

Clinical studies have demonstrated that patients with gain-of-function (GOF) mutations in *STAT1* or *STAT3* are predisposed to invasive fungal infections, and treatment of chronic mucocutaneous candidiasis (CMC) patients with the JAK inhibitor ruxolitinib effectively alleviates their clinical symptoms[313]. Furthermore, JNK1 inhibitors (such as SP600125 and JNK-IN-8) have shown significant antifungal activity in both animal models and cellular assays[363]. In parallel, researchers are investigating methods to potentiate antifungal signaling by alleviating inhibitory mechanisms within innate immune pathways. For example, disrupting Dok3 mediated inhibition of Card9 *via* a synthetic short peptide markedly enhances neutrophil antifungal function[364]. In addition, a short peptide modified with the N-terminal 18 amino acids of STING can block STING mediated inhibition of the downstream kinase Syk, thereby reducing the risk of disseminated fungal infection in murine models[365]. Moreover, adoptive transfer of immune cells-including neutrophils, antigen-specific T cells, and natural killer (NK) cells has been shown to augment further the host's ability to clear fungal pathogens[351] (Table 4).

## 17. Reuse of clinical drugs in the antifungal field

In addition to the *de novo* synthesis of new compounds and the use of natural bioactive extracts, researchers have increasingly focused on optimizing the delivery methods or formulations of existing antifungal drugs, as well as combining them with non-antifungal agents to increase therapeutic efficacy. Although anticancer, antibacterial, and antiviral drugs are not designed primarily to target fungi, some have demonstrated potential antifungal activity through cross-domain effects. Compared with novel drug development, drug repurposing offers significant advantages in the treatment of invasive fungal infections. First, it shortens the research and development timeline, reduces costs, and accelerates clinical translation, thereby addressing the growing challenge of drug resistance. Second, as the safety profiles and pharmacokinetic properties of these drugs are already well characterized, their clinical application involves fewer uncertainties, facilitating dose optimization and minimizing potential toxicity risks. Moreover, certain repurposed drugs may exhibit novel mechanisms of action or synergistic effects with antifungal agents, helping to overcome resistance and expand therapeutic options, particularly for multidrug-resistant fungal infections and immunocompromised patients. These drugs may exert their antifungal effects by enhancing host immune responses, inhibiting pathogen immune evasion, or directly disrupting fungal growth, offering potential adjunctive treatment strategies for patients with immunodeficiency or antifungal drug resistance.

### *17.1. Antifungal potential of antimicrobial agents*

Traditional antibacterial agents primarily include beta-lactams (such as penicillins and cephalosporins), sulfonamides, tetracyclines, aminoglycosides, macrolides, chloramphenicol, lincosamides, and early-generation quinolones. These drugs exert their antibacterial effects by inhibiting cell wall synthesis, disrupting cell membrane integrity, inhibiting protein synthesis, and interfering with nucleic acid metabolism. Numerous studies have

reported that some antibacterial agents possess broad-spectrum antifungal activity, and their use, either as monotherapy or in combination with existing antifungal drugs, may further enhance antifungal efficacy[366,367].

#### *17.1.1. Tetracycline antibiotics*

Minocycline is a semi-synthetic, second-generation tetracycline antibiotic widely used to treat various infectious and non-infectious conditions. Its antibacterial effect is primarily mediated by binding to the 16S rRNA and S7 proteins of the bacterial 30S ribosomal subunit, which alters the ribosomal conformation and prevents aminoacyl-tRNA from accessing its binding site, thereby inhibiting protein synthesis.

In addition to its antibacterial properties, minocycline has demonstrated antifungal activity against fluconazole-resistant *Candida* species, including *C. albicans*, *C. tropicalis*, and *C. glabrata*[368]. Several investigations have demonstrated that minocycline, when coadministered with conventional antifungal agents such as amphotericin B, itraconazole, posaconazole, and voriconazole-yields increased antifungal activity[369-372]. In these organisms, the minimum inhibitory concentrations (MICs) range from 4 to 427 μg/mL, reflecting considerable variability among strains. When combined with fluconazole, minocycline significantly reduces the MIC of fluconazole, decreasing it from 512 to 2 μg/mL with a fractional inhibitory concentration index (FICI) as low as 0.035, indicating a strong synergistic effect[370]. In a *Candida albicans* biofilm model, treatment with minocycline alone led to a reduction in biofilm activity of more than 50%, and its combination with fluconazole further enhanced the effect, resulting in an approximately 70% reduction in fluorescence intensity[370]. Mechanistic studies suggest that the antifungal action of minocycline may result from enhanced fluconazole penetration into biofilms and the induction of intracellular calcium release rather than from changes in fluconazole uptake or efflux.

#### *17.1.2. Macrolide antibiotics*

Macrolide antibiotics have traditionally been regarded as protein synthesis inhibitors that exhibit broad-spectrum antibacterial activity, particularly against Gram-positive cocci and atypical pathogens. In addition, studies have demonstrated that macrolides possess immunomodulatory properties; their role in regulating excessive inflammatory responses has been extensively investigated, and they have been shown to activate innate immune responses, for instance, by inhibiting neutrophil migration[373], regulating the differentiation of monocytes into macrophages, and modulating macrophage function[374,375].

Recent studies have indicated that macrolide antibiotics can impede capsule formation in *Cryptococcus* species while simultaneously enhancing the host immune response. In particular, combined administration of clarithromycin (CAM) and azithromycin (AZM) markedly diminishes capsule thickness and lowers the capsule polysaccharide content in *Cryptococcus gattii* and other emerging strains[376]. CAM-treated *C. gattii* cells exhibit increased susceptibility to oxidative stress induced by $H_2O_2$ as well as to neutrophil-mediated phagocytic killing. Moreover, exposure to CAM enhances the uptake of *C. gattii* by murine macrophages and is associated with a significant increase in tumor necrosis factor-$\alpha$ (TNF-$\alpha$) production. Additionally, CAM treatment results in the dephosphorylation of Hog1, a key regulator within the mitogen-activated protein kinase (MAPK) signaling pathway and substantially reduces the mRNA levels of *LAC1 and LAC2*, genes linked to cell wall integrity and melanin synthesis. These findings suggest that CAM may exert its antifungal effects by modulating MAPK signaling and downregulating virulence gene expression, thereby bolstering host immune defenses[376].

#### *17.1.3. Fluoroquinolones*

Fluoroquinolones constitute a group of synthetic antimicrobial agents with broad-spectrum activity. Their primary mode of action involves the inhibition of DNA topoisomerase II, an enzyme exclusive to prokaryotic organisms. This inhibition disrupts the DNA supercoiling process, ultimately resulting in irreversible damage to bacterial chromosomes. Owing to their highly selective toxicity against prokaryotes, combined with high oral bioavailability and extensive tissue distribution (particularly achieving elevated concentrations in prostate and lung tissues), fluoroquinolones play a significant role in conventional antibacterial therapy. Moreover, several studies have demonstrated that fluoroquinolones also exhibit antifungal activity[377,378].

Recent studies have demonstrated that when administered as a 0.5% ophthalmic solution, both moxifloxacin and gatifloxacin exhibit potent antifungal activity, achieving inhibition rates exceeding 95% against *Candida* species[379]. Moreover, several fluoroquinolones have been shown to potentiate the efficacy of conventional antifungal agents against *Candida albicans* and *Aspergillus fumigatus*[380-382], whereas the combination of ciprofloxacin with azole antifungals has synergistic effects on *Cryptococcus neoformans*[383]. Clinically, despite the limited reports on quinolone-based interventions for fungal keratitis, documented cases indicate that topical moxifloxacin monotherapy can effectively resolve this condition, highlighting the importance of achieving high local drug concentrations in ocular fungal infections[384]. Mechanistic investigations have established that the primary target of fluoroquinolones in yeast is topoisomerase II[385,386]. Further research suggested that resistant forms of yeast topoisomerase II may harbor amino acid substitutions analogous to the mutations observed in the *gyrA* gene of *Escherichia coli*[387-389]. Additionally, the distinct structural and functional differences between yeast and mammalian type II topoisomerases likely underlie the antifungal activity of fluoroquinolones and their selective toxicity toward prokaryotic targets.

## 18. Antifungal potential of antineoplastic drug components

### *18.1. AR-12*

AR-12, a derivative of the antitumor drug celecoxib, was initially developed for antitumor therapy and entered clinical studies. However, recent findings have demonstrated that it also exhibits fungicidal activity against *Cryptococcus neoformans* and *Candida albicans*[390,391]. AR-12 exerts its antifungal effects through two mechanisms. Firstly, it has been established that this substance functions as an ATP-competitive, time-dependent inhibitor of yeast acetyl-CoA synthetase. This key enzyme has a vital function in facilitating microbial growth. It has been established that the inhibition of the enzyme mentioned above may result in the occurrence of fungal autophagy, in addition to the consequent loss of cellular integrity. Second, AR-12 downregulates the expression of host molecular chaperone proteins, which enhances host immune responses[392].

AR-12 has demonstrated substantial antifungal efficacy against a broad spectrum of fungal pathogens, including yeasts, molds,

and dimorphic species, as well as *Candida albicans* strains that are resistant to both azoles and echinocandins[391]. In an AJ/Cr murine model of cryptococcal meningitis, treatment with AR-12 markedly enhanced the therapeutic effect of fluconazole[391].

### *18.2. CBR-5884*

CBR-5884 represents a phosphoglycerate dehydrogenase inhibitor that was originally developed for the purpose of blocking the synthesis of folitropic serine. Evidence has emerged demonstrating the significant antitumor activity of CBR-5884 against melanoma and breast cancer cell lines[393]. Although the antitumor properties of CBR-5884 have been extensively studied, recent studies have indicated its potential for use in antifungal applications. Specifically, CBR-5884 has been demonstrated to interfere with phosphatidylserine (PS) synthesis by competitively binding to the serine binding site of Cho1 in fungal cells. This mechanism significantly inhibits the growth and function of *Candida albicans*, thereby providing a rationale for further studies of CBR-5884 in the antifungal field[51].

### *18.3. MitoTam*

MitoTam is an anticancer drug developed *via* a mitochondrial-targeting strategy. Its core active component is a derivative of tamoxifen, and it utilizes the triphenylphosphonium cation ($TPP^+$) as a mitochondria-targeting carrier[394]. MitoTam exerts its antitumor effects by impairing mitochondrial respiratory chain complex I, which in turn elevates the intracellular production of superoxide radicals and activates apoptotic pathways[395,396]. Clinical investigations have revealed that MitoTam has pronounced antitumor efficacy, especially in the treatment of renal cell carcinoma, breast neoplasms, and triple-negative breast cancer[397].

Investigations have revealed that even at submicromolar concentrations, MitoTam exerts potent cytotoxic effects on key pathogenic eukaryotes. In particular, concentrations below the effective concentration 50 ($EC_{50}$) inhibit the proliferation of *Candida albicans* and *Cryptococcus neoformans*, potentially by inducing the upregulation of multiple drug efflux pump genes in *Candida*[394]. The antifungal efficacy of this compound is attributed to its unique mechanism of targeting mitochondria in conjunction with its broad-spectrum inhibitory activity against various pathogens.

## 19. Antifungal potential of antivirals

### *19.1. K21*

K21 is a quaternary ammonium compound anchored to a silica dioxide carrier and features a tetraethoxysilane moiety within its structure[398]. It has been shown to exert notable inhibitory effects against several oral pathogens, including *Porphyromonas gingivalis*, *Escherichia coli*, *Streptococcus* species, *Actinomyces naeslundii*, and *Enterococcus faecalis*[399-403]. Moreover, evidence suggests that K21 possesses antiviral properties against herpes simplex virus type 1 (HSV-1), human herpesvirus 6A (HHV-6A), and human herpesvirus 7 (HHV-7), acting either by suppressing viral replication or by directly targeting the viral envelope[404,405].

Additional studies have demonstrated that a concentration of 62.48 μg/mL K21 can eradicate 99.9% of *Candida albicans* and *Candida glabrata* within 2 h; even at half or one-quarter of the minimum inhibitory concentration (MIC), the compound maintains significant antifungal activity. When combined with fluconazole, K21 exhibits pronounced synergistic effects against various *Candida* strains, including those resistant to fluconazole in oral infections. Mechanistic investigations indicate that K21 primarily mediates its fungicidal effect by disrupting the fungal cell membrane mechanism similar to that of amphotericin B but distinct from fluconazole's inhibition of ergosterol synthesis[406]. Consequently, the coadministration of K21 with fluconazole appears to synergistically compromise membrane permeability and interfere with normal cell division, thereby enhancing antifungal efficacy.

### *19.2. Ribavirin*

Ribavirin, a synthetic purine nucleoside analog with broad-spectrum antiviral properties, disrupts viral replication by interfering with nucleotide metabolism. It is commonly employed in the treatment of viral infections, including those caused by respiratory syncytial virus (RSV), hepatitis C virus (HCV), and hemorrhagic fever viruses such as Lassa virus.

Recent investigations have revealed that acting as an inhibitor of inosine monophosphate dehydrogenase (IMPDH), ribavirin exhibits potent antifungal efficacy against *Candida albicans* both as monotherapy and in combination with fluconazole (FLC)[407,408]. Experimental findings indicate that the minimum inhibitory concentration ($MIC_{80}$) for ribavirin against *C. albicans* falls between 2 and 4 μg/mL, whereas for fluconazole-resistant strains, the $MIC_{80}$ reaches approximately 8 μg/mL levels that align with clinical safety parameters. In a *Galleria mellonella* infection model, the adjunctive use of ribavirin with fluconazole significantly enhanced therapeutic outcomes and reduced tissue damage attributable to fluconazole-resistant *C. albicans*, thereby substantiating a synergistic antifungal effect. Mechanistic research suggests that ribavirin may exert its antifungal action by inhibiting biofilm formation, diminishing phospholipase activity, and suppressing hyphal transformation, independent of alterations in drug absorption or efflux[408]. Furthermore, ribavirin shows synergistic activity when combined with other azole antifungals, such as itraconazole and posaconazole, although no such synergy has been observed with 5-fluorocytosine[407].

## 20. Conclusions and future perspectives

Recent advances in medicine have led to the development of innovative antifungal agents that demonstrate robust clinical efficacy in managing invasive fungal infections. This review provides a comprehensive overview of emerging antifungal therapeutics and highlights their diverse mechanisms of action. The discussion encompasses recent progress in targeting fungal cell walls, cell membranes, mycelia, and biofilm structures. For example, inhibitors directed against cell wall biosynthetic enzymes, such as glucan synthase and chitin synthase, have been intensively investigated due to their high specificity, whereas structural modifications have markedly improved the safety profiles of compounds acting on the cell membrane. In addition, agents that impede hyphal and biofilm formation are increasingly recognized as promising therapeutic options for multidrug-resistant pathogens. Many of these compounds are currently undergoing late-stage clinical trials,

representing new drug classes with innovative mechanisms and distinctive pharmacodynamic profiles. Emerging antifungal agents-including manogepix, olorofim, T-2307, and VL-2397-have exhibited robust activity in both *in vitro* and *in vivo* models against isolates resistant to azoles or echinocandins, as well as species with intrinsic resistance to conventional antifungals. Moreover, several agents share similar targets with established drugs but have been optimized to improve their pharmacokinetic properties; for example, rezafungin has been chemically modified to increase metabolic stability, whereas ibrexafungerp and MAT2203 offer viable alternatives for oral administration. Additionally, opelconazole facilitates targeted pulmonary delivery, and oteconazole has been engineered to minimize drug−drug interactions and adverse effects. Collectively, these innovations not only improve the treatment of invasive fungal infections but also expand the therapeutic options available to clinicians, enabling more tailored and individualized antifungal strategies.

Despite significant progress in antifungal research, invasive fungal infections continue to pose substantial clinical challenges due to their high morbidity, mortality, and increasing drug resistance. These issues are particularly pronounced in the realms of early diagnosis, the elucidation of resistance mechanisms, and the formulation of personalized treatment strategies. Future research should prioritize the identification of novel intracellular fungal targets and the development of multitarget agents. Numerous potential targets, both intracellular and extracellular, are currently under investigation; these include enzymes involved in nucleic acid metabolism, such as pyrimidine synthases and DNA repair proteins, as well as components of stress response and autophagy pathways. In addition, targeting fungal virulence factors, the cytoskeleton, and the complex interactions between fungal pathogens and the host immune system offers promising new avenues for therapy. Enhancing the molecular design and delivery methods of existing drugs is also expected to improve their safety profiles and patient adherence. Ongoing efforts in these areas are anticipated to yield significant breakthroughs in both the diagnosis and treatment of invasive fungal infections, thereby providing safer, more effective therapeutic options and advancing the field toward precision medicine and personalized care[277].

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## Author contributions

Xueni Lu contributed to the data collection and organization, writing-original draft preparation, figure and table drawing. Jianlin Zhou is primarily responsible for reference proofreading and organization, charting. Lingyun Feng, Yi Ming, Yuan Wang and Ruirui He collected and provided part of the literature data. Yangyang Li, Bo Zeng and Yanyun Du contributed to the manuscript proofreading and correction. Chenhui Wang contributed to determining the general direction and objectives of the research, and revision of the manuscript.

## Conflicts of interest

The authors declare no conflicts of interest.

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