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The evolution of antifungal therapy: Traditional agents, current challenges and future perspectives

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ABSTRACT

Fungal infections kill more than 3 million people every year. This high number reflects the significant challenges that treating these diseases worldwide presents. The current arsenal of antifungal drugs is limited and often accompanied by high toxicity to patients, elevated treatment costs, increased frequency of resistance rates, and the emergence of naturally resistant species. These treatment challenges highlight the urgency of developing new antifungal therapies, which could positively impact millions of lives each year globally. Our review offers an overview of the antifungal drugs currently available for treatment, presents the status of new antifungal drugs under clinical study, and explores ahead to future candidates that aim to help address this important global health issue.

1. Introduction

The annual number of global deaths toll from fungal diseases has been estimated to approximately 3.75 million, doubling earlier figures that ranged from 1.5 to 2 million deaths per year. Among these fatalities, approximately 68 % (or 2.5 million) are directly attributed to fungal infections (Denning, 2024). These alarming numbers, stem from vulnerable populations, underreported cases and low global awareness of fungal infections, which receive less attention than other infectious diseases, such as malaria and tuberculosis, despite exhibiting higher mortality rates (de Oliveira et al., 2023; Denning, 2024; Rodrigues and Nosanchuk, 2020).

Currently, antifungal options are limited and associated with high toxicity, increasing resistance, and substantial costs, representing a significant burden on public health systems (Fisher et al., 2022; Kneale et al., 2016; Rodrigues and Nosanchuk, 2020; Stewart and Paterson, 2021). Additionally, there is growing concern with the emergence of resistant species, a critical situation that could further complicate this scenario (Forsberg et al., 2019; Hoenigl et al., 2022; Lockhart et al., 2023, 2017; Sarma and Upadhyay, 2017). In this context, advancing the development of more effective and safer antifungals is an urgent priority.

Prioritizing research and investments in this field is essential for global public health. Expanding antifungal options and increasing awareness are critical for mitigating the devastating impact of fungal diseases and saving millions of lives. Our review provides a comprehensive overview of antifungal drugs, discusses current treatments for mycosis and potential strategies such as drug repurposing, nanotechnology-based approaches, antifungal peptides, combination therapy, and immunotherapy.

2. Traditional use and current resistance to antifungal drugs

2.1. Polyenes

As discovered in 1949 by Elizabeth Lee Hazen and Rachel Fuller Brown, polyenes were the first class of antifungal drugs used clinically (Carmo et al., 2023; Carolus et al., 2020; Vanreppelen et al., 2023). Owing to their broad-spectrum antifungal activity and low resistance rates, they remain the gold standard for treating systemic fungal infections and dermatomycoses, with amphotericin B (AmB), nystatin and natamycin, the three most widely used (Carmo et al., 2023; Carolus et al., 2020).

Nystatin, the first patented polyene used to treat fungal infections, is

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now limited to topical use owing to its poor solubility, low bioavailability and severe side effects. It is primarily used for treating cutaneous and mucosal *Candida* infections (Lyu et al., 2016; Samaranayake et al., 2009). Similarly, natamycin, another topical polyene, is commonly recommended for ocular fungal infections, including keratitis (Cabrera-Aguas et al., 2022).

AmB has been a key treatment for systemic fungal infections for nearly six decades (Cavassin et al., 2021). It is effective against *Histoplasma* spp., *Aspergillus* spp., *Fusarium* spp., *Cryptococcus* spp., *Candida* spp., *Blastomyces* spp., *Coccidioides* spp., *Mucor* spp. *and Sporothrix* spp., which are used in both first- and second-line therapies (Barros et al., 2023; Boutin and Luong, 2024; Cavassin et al., 2021; de Oliveira Santos et al., 2018; Goralska et al., 2018; Iyer et al., 2021). Owing to its poor gastrointestinal absorption, AmB is administered intravenously, often in combination with other antifungal drugs such as flucytosine or fluconazole for the treatment of *Cryptococcus* and *Candida* infections, particularly in cases of azole resistance and severe cases such as central nervous system (CNS) dissemination, as well as HIV and recent transplant patients. For aspergillosis and mucormycosis, AmB is combined with echinocandins or azoles, respectively (Boutin and Luong, 2024; Cavassin et al., 2021).

The efficacy of AmB lies in its unique mechanism of action: binding to ergosterol, a vital fungal cell membrane component (Carolus et al., 2020). Ergosterol maintains membrane integrity and supports processes such as endocytosis, cell division, and fungal pathogenicity (Carolus et al., 2020; Choy et al., 2023; Heese-Peck et al., 2002), making it a critical drug target. By binding to sterols in the membrane, AmB forms pores, causing ion leakage and intracellular damage. It also generates free radicals, inducing oxidative stress and cellular damage (Fig. 1). This combination of mechanisms of action ensures its fungicidal effect (Carolus et al., 2020; Cavassin et al., 2021).

AmB is available in various formulations. The original AmB-deoxycholate is effective but highly toxic, with side effects such as nephrotoxicity, fever, nausea, vomiting and headaches (Carmo et al., 2023; Laniado-Laborín and Cabrales-Vargas, 2009). Newer formulations, such as the AmB lipid complex (ABLC), and liposomal AmB (L-AmB), reduce toxicity, allow the administration of higher doses, and improve treatment outcomes, representing major advances in AmB therapy (Adler-Moore and Proffitt, 2008; Botero Aguirre and Restrepo Hamid, 2015). Ongoing research into optimizing these formulations is the key to ensuring that polyenes remain an essential tool in managing life-threatening fungal diseases.

AmB resistance is rare and linked to mutations in the ergosterol biosynthesis pathway, which, by depleting of ergosterol from the membrane leads to the accumulation of different sterols (Fig. 2). However, resistance often results in fitness trade-offs, such as increased stress sensitivity and vulnerability to febrile temperatures and enhanced susceptibility to neutrophil-mediated killing (Lee et al., 2023, 2021). For instance, In *Candida* spp. resistance involves mutations in genes like ERG2, ERG3, ERG6, and ERG11. In *C. neoformans* only one resistant clinical isolate has been reported, linked to a mutation in ERG3 (Lee et al., 2023).

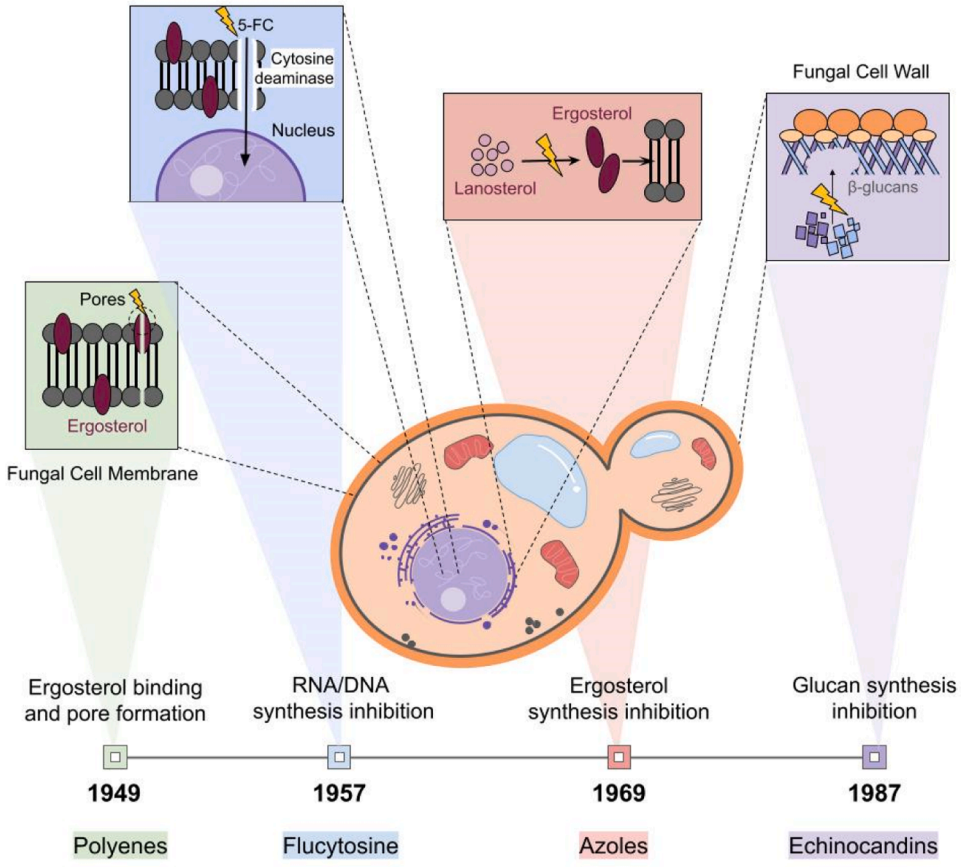

Fig. 1. Representation of classical antifungal drugs, their mechanisms of action and respective dates of discovery. Polyenes (1949): bind to ergosterol in the fungal cell membrane, forming pores that compromise cell integrity. Flucytosine (1957): once metabolized into 5-fluorouridine triphosphate, incorporates into fungal RNA, replacing uridylic acid and inhibiting RNA/DNA synthesis. Azoles (1969): inhibit the activity of the enzyme lanosterol 14-α-demethylase, disrupting ergosterol synthesis and compromising membrane integrity. Echinocandins (1987): bind to the β-(1,3)-d-glucan synthase subunit Fks1p, blocking its activity and inhibiting the synthesis of β-(1,3)-d-glucan, a critical structural component of the fungal cell wall. The cellular targets of each class are highlighted in a schematic representation of the fungal cell.

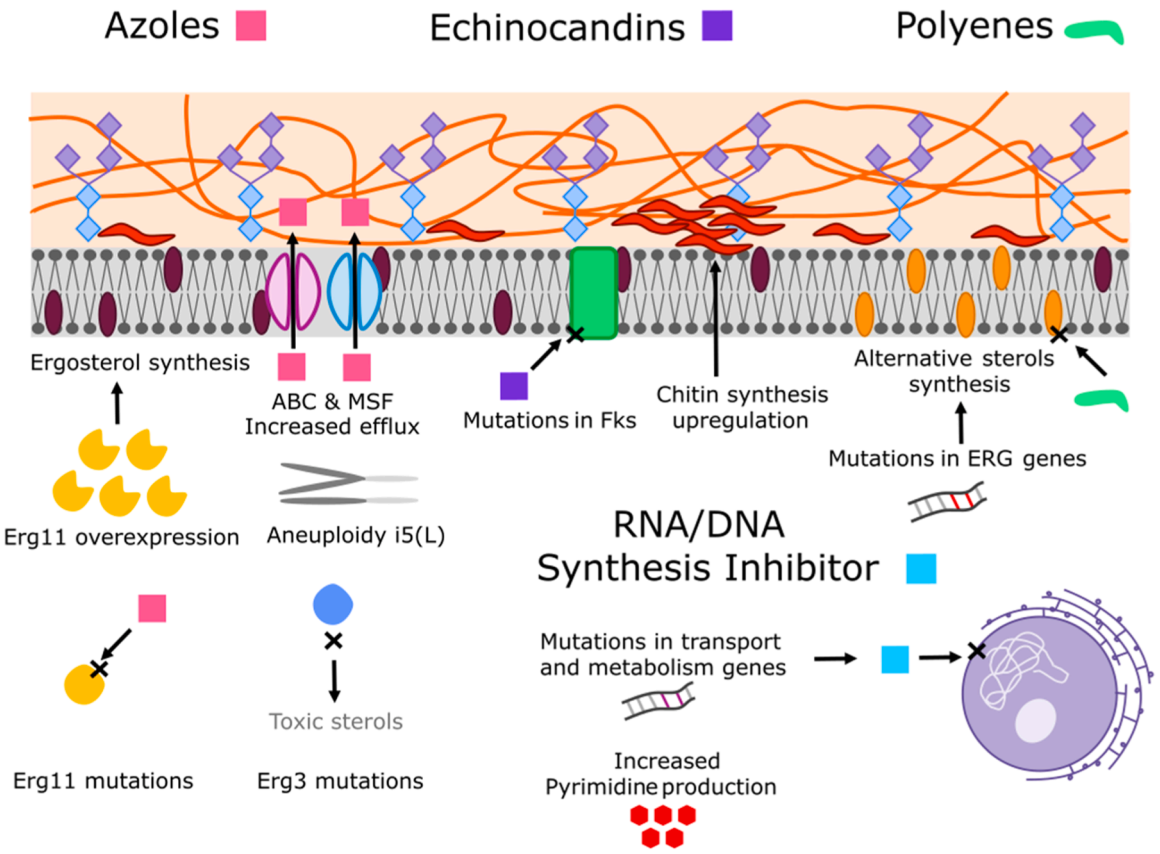

Fig. 2. Representation of the main antifungal resistance mechanisms. Each pathway highlights specific genetic mutations and cellular processes that contribute to resistance. Azole resistance occurs when Erg11 is overexpressed counteracting the effect of the azole and permitting ergosterol synthesis, additionally Erg11 mutations impede the binding of the azole; mutations in Erg3 prevent the accumulation of other toxic sterols; aneuploidies in chromosome 5, forming an isochromosome i5(L) lead to an increased number of copies of Erg11; the increased presence of ABC and MSF transporters reduces the intracellular drug concentration. Echinocandins resistance arises when Fks is mutated blocking the echinocandin binding and chitin synthesis upregulation, which helps to maintain the cell wall structure. Polyenes resistance emerges when different ERG genes are mutated, allowing the synthesis of alternative sterols shifting the cell membrane composition. RNA/DNA synthesis inhibitor resistance originates when transport and metabolism genes are mutated, impeding the importation of the drug to the nucleus; the increased pyrimidine production, diminishes the effect of the drug.

2.2. *Flucytosine*

Flucytosine (5-fluorocytosine [5-FC]), a synthetic pyrimidine analog initially developed for antitumor therapies, was first studied as an antifungal agent in 1968 (Sigera and Denning, 2023; Wall and Lopez-Ribot, 2020). Despite its potential, 5-FC is unavailable in Canada, Mexico and most of South America and Africa (Ngan et al., 2022; Sigera and Denning, 2023).

5-FC is included in fungal therapeutic guidelines but has a limited spectrum compared with that of polyenes. It is effective against *Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida lusitaniae* and *Cryptococcus neoformans*. However, it does not target relevant fungal pathogens such as *Aspergillus spp*., Mucorales, *Coccidioides* and *Histoplasma*, limiting its clinical application (de Oliveira Santos et al., 2018; Sigera and Denning, 2023; Spadari et al., 2020).

Available in oral or intravenous forms, 5-FC enters fungal cells via cytosine permease and is converted into 5-fluorouracil (5-FU) (Carmo et al., 2023). From this point, 5-FU is metabolized into 5-fluorouridine triphosphate, which can incorporate the fungal ribonucleic acid (RNA), replace uridylic acid and thereby inhibit protein synthesis (Fig. 1). Additionally, 5-FU can be converted to fluoro-deoxyuridine monophosphate, which interferes with DNA synthesis by blocking thymidylate synthetase, a key enzyme in this process (Fig. 1). Since human cells lack cytosine permease, 5-FC presents reduced toxicity, although, some side effects such as leukopenia, nausea, vomiting, bone marrow suppression, thrombocytopenia, anemia and hepatitis, can still occur during treatment (Carmo et al., 2023; Houšť et al., 2020; Sigera and Denning, 2023).

Despite its efficacy, 5-FC faces significant challenges in clinical practice because of the rapid development of resistance (Bhattacharya et al., 2020; Sigera and Denning, 2023; Yang et al., 2023), often due to mutations or loss of enzymes involved in its transport and metabolism (*e.g.*, FCY1, FCY2 or FUR1) or increased pyrimidine production, as observed in *Saccharomyces cerevisiae* and *Candida* spp. (Czajka et al., 2023) (Fig. 2). As a result, 5-FC is rarely used as a monotherapy and is primarily recommended in combination with other antifungals. For invasive *Candida* infections, it is paired with AmB or voriconazole, while its combination with AmB is standard for the treatment of cryptococcal meningitis (de Oliveira Santos et al., 2018; Spadari et al., 2020).

2.3. *Azoles*

Azoles are a widely used class of antifungals, with many drugs being developed over the years and new drugs still being developed (Shafiei et al., 2020). The mechanism of action involves inhibiting lanosterol 14-α-demethylase (LDM), which is essential for ergosterol synthesis (Fig. 1), disrupting the integrity of fungal cell membranes, leading to the accumulation of sterol intermediates that are toxic to the cell, impacting its growth and subsequent death (Maertens, 2004).

The first generation of azoles, clotrimazole, miconazole and econazole, is characterized by an imidazole backbone and is used mainly as a topical therapeutic option. Clotrimazole and miconazole were originally

available in oral and intravenous forms, respectively, but owing to severe side effects and pharmacokinetic challenges, they were reformulated for topical use, being commonly used for skin infections such as dermatomycoses and superficial *Candida* infections, such as oropharyngeal and vulvovaginal candidiasis (Carmo et al., 2023). Ketoconazole was introduced for systemic fungal infections but has limitations such as poor blood-brain barrier penetration, poor efficacy in immunocompromised patients, hepatotoxicity, drug interactions and dose-related side effects (Carmo et al., 2023; Gupta and Lyons, 2015; Maertens, 2004).

This led to the development of triazoles, which have a triazole ring instead of an imidazole, improving water solubility and central nervous system (CNS) penetration and reducing side effects. Triazoles, such as fluconazole and itraconazole are now available for both oral and intravenous applications and have a broad activity spectrum (Carmo et al., 2023; Shafiei et al., 2020).

Fluconazole has emerged as a key treatment because of its enhanced activity, selectivity, improved pharmacokinetic profile with enhanced CNS penetration, lower serum protein binding, and safety when it is administered at high doses (Shafiei et al., 2020). Fluconazole is approved for treating patients with cryptococcal meningitis, various forms of candidiasis and coccidioidomycosis, although it is not effective against filamentous fungi (Carmo et al., 2023; Maertens, 2004; Nett and Andes, 2016). Over time, however, resistance to fluconazole has emerged, particularly in *Candida* and *Cryptococcus* species, raising concerns about its long-term efficacy (Berkow and Lockhart, 2017; Bongomin et al., 2018; Cheong and McCormack, 2013; Lockhart et al., 2023). Itraconazole, another triazole with a broader spectrum of activity against fungi such as *Aspergillus* spp., *Trichosporon* spp., *Fusarium* spp., was later introduced (Nett and Andes, 2016; Shafiei et al., 2020). However, its ability to penetrate the CNS and associated side effects may limit its use compared with fluconazole (Carmo et al., 2023).

Voriconazole, a triazole with a fluoropyrimidine ring in its structure, has high bioavailability and pharmacokinetics similar to those of fluconazole and its being used for invasive aspergillosis and *Candida* and *Cryptococcus* infections (Carmo et al., 2023; Chatelon et al., 2019). However, its clinical use is complicated by side effects, warnings regarding drug interactions and recently registered *Aspergillus fumigatus* resistance development (Chatelon et al., 2019; Lockhart et al., 2023). Posaconazole is another significant improvement in the triazole class, with a broader spectrum of activity, covering *Zygomycetes, Mucorales* and *Scedosporium*, and is recommended for the prophylaxis of invasive fungal species in specific clinical cases (Leung et al., 2015; Maertens, 2004). Isavuconazole (ISA), one of the most recent triazoles, provides antifungal coverage similar to that of voriconazole and posaconazole, with a safer profile and fewer drug interactions, making it a valuable addition to antifungal treatment options (Ellsworth and Ostrosky-Zeichner, 2020; Lewis et al., 2022).

Azole resistance often arises from mutations in the ERG11 gene, which encodes the target enzyme 14-α-demethylase in yeasts such as *Candida* spp. and cyp51 in molds (Czajka et al., 2023; Lee et al., 2023), leading to a reduced binding of the azole to its active site in the enzyme. More than 140 distinct Erg11 amino acid substitutions have been reported to cluster in hotspot regions in *C. albicans*, in contrast, *C. neoformans* has fewer ERG11 mutations described in azole resistant clinical isolates (Fig. 2) (Lee et al., 2023). In *A. fumigatus,* there are two genes encoding Cyp51 isoenzymes (cyp51A and cyp51B), and mutations in cyp51A cause triazole resistance, whereas mutations in cyp51A confer resistance to voriconazole. Duplications in the *cyp51A* gene promoter in combination with certain amino acid substitutions appear in environments where azoles are used in agribusiness and are isolated from patients in the clinic who have never been exposed to antifungal drugs (Lee et al., 2023).

Mutations in other genes, such as ERG3 and ERG6 can also contribute to resistance, particularly in *Candida* species (Gregor et al., 2023). Cross-resistance between echinocandins and azoles has been observed, often due to mutations in ERG3, altered sterol composition, and reduced efficacy of both drug classes (Bhattacharya et al., 2020; Lee et al., 2021). The overexpression of transcriptional regulators such as UPC2 due to azole exposure can confer resistance to azoles (Czajka et al., 2023; Dunkel et al., 2008).

Increased efflux is another resistance mechanism, mediated by the ABC (ATP-binding cassette transporters) and MSF transporters (major facilitator superfamily transporters) (Fig. 2). The export of the drug out of the cell reduces the intracellular drug concentration, lowering its effectiveness and enhancing cell survival (Czajka et al., 2023). The overexpression of the ABC transporters Cdr1 and Cdr2 in *C. albicans* is caused by the development of chromosome 3 trisomies, which reduce drug efficacy. This overexpression can be further induced by gain-of-function (GOF) mutations resulting from the overexpression of transcriptional activator genes such as TAC1 and TAC1B and activating mutations in MMR1 and MMR1A in *C. albicans* and *C. auris*, respectively (Czajka et al., 2023; Lee et al., 2023). In *C. neoformans*, the overexpression of multidrug efflux transporters is mediated by the ABC transporter Afr1. In *A. fumigatus*, the overexpression of multidrug efflux transporters is mediated by the ABC transporter AtrF, and the transcription factor AtrR regulates *cyp51A* (Fig. 2) (Lee et al., 2023).

Genomic alterations such as chromosomal duplications and copy number variations, also contribute to azole resistance. In *C. albicans*, duplication of the left arm of chromosome 5 enhances resistance by increasing the number of copies of ERG11 and its regulatory transcription factor (Lee et al., 2023). In *C. auris*, supernumerary chromosomes promote resistance (Narayanan et al., 2022), whereas chromosomal translocations and duplications are common resistance mechanisms in *C. glabrata*. Temporary disomies of chromosome 1 are the most common mechanism of heteroresistance in *C. neoformans*. In *A. fumigatus* horizontal gene transfer of chromosomes can lead to voriconazole resistance (Lee et al., 2023).

2.4. Echinocandins

Echinocandins, discovered in the 1970s, constitute an important class of antifungal agents, with three drugs currently approved for clinical use: caspofungin, micafungin and anidulafungin (Mroczyńska and Brillowska-Dąbrowska, 2020). Originally derived from filamentous fungi and then semisynthetically produced, these compounds have a complex structure and are used to treat certain invasive fungal infections. Echinocandins are nonribosomal lipopeptides, with cyclic hexapeptides and a lipophilic side chain (Hüttel, 2021; Ivanov et al., 2022). They are water soluble, formulated as lyophilized powders, and administered intravenously due to poor gastrointestinal absorption (Szymański et al., 2022). Resistance remains low but is an emerging concern (Pristov and Ghannoum, 2019; Satish and Perlin, 2019).

Unlike other antifungals, echinocandins target the fungal cell wall, specifically β-(1,3)-d-glucan synthase, a key structural of fungal cells. They inhibit β-(1,3)-D-glucan synthase through binding to the enzyme subunit Fks1p, blocking its activity and consequently inhibiting the biosynthesis of β-(1,3)-D-glucan, leading to the destabilization of the fungal cell wall and causing cell death (Fig. 1). This mechanism of action has a limited sensitivity to some species, restricting their spectrum of action (Mroczyńska and Brillowska-Dąbrowska, 2020; Szymański et al., 2022). Due to the high composition of glucans in the fungal cell wall and their absence in mammalian cells, their mechanism of action results in high efficacy and fewer toxic effects. Clinically, echinocandins are first-line treatments for candidiasis or coadministered with another antifungal agent to treat aspergillosis, with no efficacy detected against *Cryptococcus, Fusarium* or *Mucorales*. Susceptible fungi include *C. albicans, C. auris, C. parapsilosis, C. krusei, A. fumigatus, A. flavus* and *A. niger* (Cândido et al., 2020; Mroczyńska and Brillowska-Dąbrowska, 2020; Szymański et al., 2022). Despite their lower toxicity, side effects such as edema, bronchospasm, dyspnea and low blood pressure may occur (Szymański et al., 2022).

The Food and Drug Administration (FDA) first approved caspofungin

in 2001 for invasive aspergillosis, candidaemia and esophageal candidiasis, including prophylaxis in high-risk patients such as those with HIV or cancer. Micafungin, which was approved in 2005, has reduced hemolytic activity and is recommended for *Candida* infections, esophageal and deep tissue candidiasis, and prophylaxis in pediatric and elderly patients (Mroczyńska and Brillowska-Dąbrowska, 2020). However, further studies are needed to assess the efficacy of each echinocandin against different *Candida* and *Aspergillus* species.

Resistance primarily arises from mutations in the β-1–3 glucan synthase enzymes FKS1 (*Candida, Cryptococcus* and *Aspergillus* spp.) and FKS2 in *C. glabrata* (Fig. 2) (Czajka et al., 2023; Lee et al., 2023). In Candida spp., point mutations in FKS1, especially in hotspot regions, confer resistance, with *C. albicans, C. tropicalis, P. kudriavzevii*, and *C. glabrata* being affected. These mutations, particularly gain-of-function (GOF) mutations in hotspot regions, can confer resistance. In *C. albicans*, a single hotspot mutation can confer resistance to all three echinocandins, although the low prevalence of FKS1 mutations is due to their detrimental effects on cell fitness, limiting their spread in the absence of echinocandin pressure (Ben-Ami et al., 2011; Lee et al., 2023). Additionally, point mutations in the PDR1 transcription factor in *C. glabrata* can also contribute to echinocandin resistance (Vu et al., 2021).

Figs. 1 and 2 illustrate, respectively, the mechanisms of action of the antifungals mentioned above and the resistance mechanisms developed by fungi against these antifungals.

3. Opportunities: new antifungal drugs in clinical trials

New antifungal agents are currently under development at different phases of clinical trials, potentially offering a new arsenal to fight fungal infections. These promising drugs target (1) nucleic acid metabolism, (2) the fungal cell membrane and (3) the fungal cell wall.

3.1. Nucleic acid metabolism

3.1.1. Olorofim

Olorofim represents a novel class of antifungal agents known as orotomides (Oliver et al., 2016), which act by inhibiting fungal dihydroorotate dehydrogenase (DHODH), an enzyme crucial for pyrimidine synthesis in fungi (Oliver et al., 2016; Rauseo et al., 2020; Sousa et al., 2021) (Fig. 3). Importantly, this drug exhibits fungal-specific action, as analogous human enzymes are unaffected, significantly reducing toxicity and rendering olorofim a potentially safe and effective option for the treatment of invasive fungal infections (Oliver et al., 2016).

Olorofim lacks broad-spectrum activity; however, recent studies

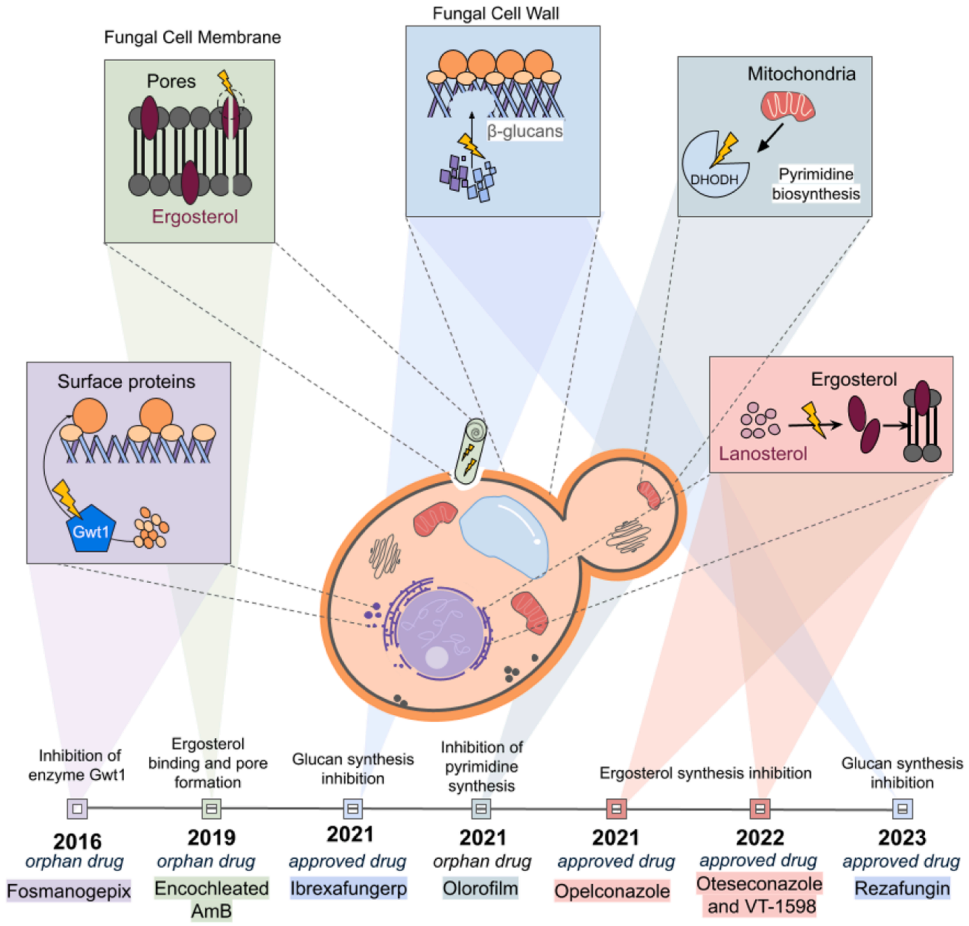

Fig. 3. Representation of recently developed antifungal drugs and their mechanisms of action. Fosmanogepix (2016): inhibits the enzyme Gwt1, which is involved in the trafficking and anchoring of mannoproteins, essential components of the fungal cell wall. Encochleated AmB (2019): shares the mechanism of action of classic AmB (ergosterol binding and pore formation), but the drug molecules are encapsulated with calcium ions within a lipid bilayer sheet, rolled into a spiral structure. Ibrexafungerp (2021): inhibits β-(1,3)-d-glucan synthase, disrupting the synthesis of β-(1,3)-d-glucan, a vital structural component of the fungal cell wall. Olorofim (2021): inhibits dihydroorotate dehydrogenase (DHODH), a critical enzyme for pyrimidine biosynthesis. Oteseconazole (2022), VT-1598 (2022), and Opelconazole (2021): inhibit lanosterol 14-α-demethylase, impairing ergosterol synthesis and compromising membrane integrity. These drugs have a mechanism of action similar to azoles but with structural and functional improvements. Rezafungin (2023): a novel echinocandin, also inhibits β-(1,3)-d-glucan synthase, targeting fungal cell wall synthesis. The figure includes a timeline highlighting the drugs' latest FDA status, either as orphan or approved drugs, alongside a schematic representation of their specific cellular targets in the fungal cell.

have demonstrated its *in vitro* activity against several clinically relevant fungal species, including dimorphic fungi such as *Sporothrix* spp. (Bombassaro et al., 2023) and *Coccidioides* spp., as demonstrated *in vivo* efficacy in a CNS coccidioidomycosis model (Nathan P Wiederhold et al., 2018b). It also shows efficacy against hyaline molds such as *Aspergillus* spp., including azole-resistant isolates (Buil et al., 2017; Oliver et al., 2016; Rivero-Menendez et al., 2019), and species within the *Fusarium solani* and *Fusarium oxysporum* complexes (Badali et al., 2021; Kirchhoff et al., 2020a). Additionally, olorofim has activity against dematiaceous fungi such as *Scedosporium* spp. and *Lomentospora prolificans* (Biswas et al., 2018; Kirchhoff et al., 2020a, 2020b; Wiederhold et al., 2017), as well as dermatophytes, including *Trichophyton* spp., *Epidermophyton* spp., and *Microsporum* spp., eradicating these fungi in an *in vivo* dermatophytosis model (Mirbzadeh Ardakani et al., 2021). However, olorofim does not exhibit activity against yeasts (Hoenigl et al., 2021), Mucorales (Georgacopoulos et al., 2021), and certain dematiaceous fungi, including *Exophiala dermatitidis* ((Kirchhoff et al., 2020a), and *Alternaria* spp. (Singh et al., 2021).

Nine phase I clinical trials of olorofim have been completed, assessing its tolerability, safety, and pharmacodynamics in single- and multiple-dosing regimens in both oral and intravenous formulations (NCT02142153, NCT0239448, NCT02342574, NCT02737371, and NCT02808741). Additionally, a study investigating the interaction of olorofim with itraconazole and rifampin was conducted (NCT04171739). Recently, a phase IIb trial was completed in patients with invasive fungal infections refractory or resistant to standard antifungal therapies (NCT03583164) (Hoenigl et al., 2021; Jacobs et al., 2022). In 2019, the FDA granted olorofim Breakthrough Therapy designation for the treatment of invasive mold infections in patients with limited or no treatment options, a designation later extended in 2020 to include CNS coccidioidomycosis refractory to standard care. Furthermore, in 2020, olorofim received orphan drug designation for the treatment of invasive aspergillosis, *Lomentospora prolificans*, and *Scedosporium* spp. infections, which was subsequently expanded to cover coccidioidomycosis. Additionally, in 2020, olorofim received the Qualified Infectious Disease Product designation for the treatment of several invasive fungal infections, including invasive aspergillosis, scedosporiosis, lomentosporiosis, coccidioidomycosis, scopulariopsis, and fusariosis (Hoenigl et al., 2021; Jacobs et al., 2022).

3.2. Fungal cell membrane

3.2.1. Oteseconazole (VT-1161) and VT-1598

Oteseconazole (VT-1161) and VT-1598 represent a new generation of azoles with reduced potential for safety issues, as they exhibit better selectivity for fungal cells (Jacobs et al., 2022; Seiler and Ostrosky-Zeichner, 2021). Unlike previous generations of azoles, which contain an imidazole or triazole moiety that binds to the human cytochrome, these new generation azoles feature a tetrazole moiety, improving target selectivity due to attenuated interactions between the metal-binding groups and the heme cofactor (Sobel and Nyirjesy, 2021) (Fig. 3).

These new-generation azole agents have shown potent activity against a broad range of *Candida* species when tested against a panel of clinical isolates of common yeast species that cause invasive infections, including *C. krusei*, fluconazole- and echinocandin-resistant *C. glabrata* and the emergent multiresistant *C. auris* (Nishimoto et al., 2019; Schell et al., 2017; Warrilow et al., 2014; Wiederhold et al., 2019a). Significant activity has also been observed against *Cryptococcus* species, which exhibit higher activity than fluconazole against *C. neoformans* and *C. gattii* isolates (Nathan P Wiederhold et al., 2018c). The activity of these new-generation azoles extends to dimorphic fungi such as *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides posadasii*, and *C. immitis* (Shubitz et al., 2015; Nathan P Wiederhold et al., 2018c; Nathan P. Wiederhold et al., 2018a), as well as filamentous fungi such as *Aspergillus* spp. (Garvey et al., 2020; Nathan P. Wiederhold et al., 2018b) and *Rhizopus* spp. (Gebremariam et al., 2017; Nathan P Wiederhold et al., 2018c), with VT-1598 being the agent that has the broadest spectrum.

These new azole drugs are at various stages of clinical trials and development status. Phase 1 studies regarding the safety and pharmacokinetics of VT-1598 have been completed (NCT04208321), and for the treatment of coccidioidomycosis, the FDA has granted QIDP, fast track, and orphan drug designation to VT-1598, for the treatment of coccidioidomycosis. A phase 2 study demonstrated the safety and efficacy of oteseconazole in treating recurrent vaginal candidiasis, leading to its designation as a QIDP and fast-Track status by the FDA (Brand et al., 2018). Subsequently, multiple Phase 3 clinical trials (NCT02267382, NCT03562156, NCT03561701, and NCT03840616) were conducted and completed, revealing the effectiveness of oteseconazole in preventing recurrent vaginal candidiasis episodes (Jacobs et al., 2022; Martens et al., 2022; Sobel, 2022).

3.2.2. PC945 (Opelconazole)

PC945 is a new generation of triazole antifungals that are first-in-class inhaled antifungal drugs (Cass et al., 2021; Murray et al., 2020). Aerosolized delivery to the lung results in higher concentrations in the epithelial lining fluid and bronchoalveolar lavage fluid (Rodvold et al., 2011) and is an important tool to fight and prevent invasive fungal infections of the sinopulmonary tract (Seiler and Ostrosky-Zeichner, 2021). Its mechanism of action is the same as that described for the azoles drugs, the inhibition of lanosterol 14α-demethylase (Hoenigl et al., 2021; Murray et al., 2020) (Fig. 3), however some structural modifications lead to chemical and physical attributes of PC945, which results in high local concentrations and prolonged lung retention (Cass et al., 2021; Hoenigl et al., 2021).

PC945 has broad-spectrum activity against yeasts and molds. Among the yeasts, PC945 showed activity against *C. albicans, C. glabrata* and *C. krusei* (Colley et al., 2017; Hoenigl et al., 2021), being more potent *in vitro* against *C. auris* than posaconazole, voriconazole, and fluconazole (Rudramurthy et al., 2019). Activity against *C. neoformans* and *C. gattii* was also described (Colley et al., 2017). Studies have shown that, compared with posaconazole, itraconazole, and voriconazole, PC945 has superior activity against *Aspergillus* spp. in both azole-susceptible and azole-resistant strains (Colley et al., 2017). PC945 lacks activity against most Mucorales; however, remarkable potency was observed against *Rhizopus oryzae* (Colley et al., 2017).

A phase 1 trial of PC945 to investigate the safety, tolerability and pharmacokinetics of single and repeated doses of PC945 has been completed; (NCT02715570) and A phase 3 trial for PC945, is expected to launch in the future, targeting adults with limited or no other treatment options for invasive pulmonary aspergillosis as part of combination antifungal therapy.

3.2.3. Encochleated AmB (MAT2203)

Encochleated AmB is a novel formulation designed for oral administration. It consists of a solid lipid bilayer sheet rolled into a spiral (Shende et al., 2019; Zarif, 2005), which consists of entrapped AmB molecules along with calcium ions. Upon uptake by phagocytic cells, a calcium gradient forms between the high concentration within the cochleate and the lower levels in the cell cytoplasm, causing the cochleate to open and release AmB into the cells (Aigner and Lass-Flörl, 2020; Shende et al., 2019; Skipper et al., 2020) (Fig. 3). This structure protects the drug from degradation and enables targeted cell delivery, leading to high concentrations inside cells that enhance the elimination of intracellular pathogens while minimizing systemic toxicity by reducing plasma levels (Aigner and Lass-Flörl, 2020; Skipper et al., 2020).

Encochleated AmB showed *in vitro* activity similar to that of deoxycholate AmB against *Candida* spp. (Santangelo et al., 2000; Zarif et al., 2000) and *Aspergillus* spp. (Delmas et al., 2002) and showed successful outcomes in immunocompromised mouse models of widespread

C. albicans infection and disseminated aspergillosis, similar to treatment with the intraperitoneal deoxycholate AmB (Delmas et al., 2002; Santangelo et al., 2000; Zarif et al., 2000). In addition, Encochleated AmB in combination with 5-FC was used in a mouse model of cryptococcal meningoencephalitis, which demonstrated strong antifungal activity with similar efficacy to the combination of 5-FC with deoxycholate AmB (Lu et al., 2019).

In 2018, a clinical trial was conducted to assess the safety and efficacy of Encochleated AmB. This initial study (NCT04031833) was a multicenter, randomized trial designed to evaluate the safety, tolerability, and efficacy of 200 mg and 400 mg doses of Encochleated AmB compared with a single 150 mg dose of fluconazole, for the treatment of moderate to severe vulvovaginal candidiasis. Although Encochleated AmB was well tolerated and no renal or hepatic toxicity was observed, it was associated with lower clinical cure rates and a greater incidence of adverse events than fluconazole. Additionally, another study on candidiasis (NCT02629419) was an open-label, dose-titration trial investigating the efficacy, safety, and pharmacokinetics of Encochleated AmB in treating mucocutaneous candidiasis infections. This trial shows improvement in clinical signs and symptoms without any evidence of renal or hepatic toxicity.

3.3. Fungal cell wall

3.3.1. Fosmanogepix

Fosmanogepix is a new and promising antifungal agent for the treatment of invasive fungal infections that targets the fungal cell wall by inhibiting the enzyme Gwt1, an inositol acyltransferase that compromises cell wall integrity, leading to growth inhibition and cell death. This enzyme plays an essential role in the trafficking and anchoring of mannoproteins (Almajid et al., 2024; Miyazaki et al., 2011; Tsukahara et al., 2003; Watanabe et al., 2012) (Fig. 3), which are essential for fungal adhesion to host cells prior to colonization and infection, the fungal cell wall, and the plasma membrane, compromising cell wall integrity and leading to fungal cell growth inhibition and death (Almajid et al., 2024; Tsukahara et al., 2003).

Fosmanogepix has broad-spectrum antifungal activity, showing strong efficacy against various common and resistant fungal species, suggesting promising therapeutic options. It effectively inhibits *Aspergillus* species, outperforming other antifungal agents, such as voriconazole, and is effective against resistant molds, such as resistant *Aspergillus* species and certain *Scedosporium/Lomentospora* strains (Alkhazraji et al., 2020; Eschenauer, 2024; Miyazaki et al., 2011; Shaheen et al., 2021). Fosmanogepix, also exhibits activity against *Candida*, including fluconazole-resistant strains such as *C. auris* and *C. albicans* with FKS mutations (Espinel-Ingroff and Wiederhold, 2024). Its efficacy extends to *C. neoformans* and *Coccidioides* species (Giamberardino et al., 2022; Trzoss et al., 2019). In animal models, Fosmanogepix has been shown to improved survival and reduced fungal burden in conditions such as *Candida* endophthalmitis, hematogenous meningoencephalitis, and invasive infections (Petraitiene et al., 2021). Notably, it has synergistic effects with fluconazole against cryptococcal meningitis (Giamberardino et al., 2022). Its activity against Mucorales is moderate, but it has demonstrates significant potential in treating pulmonary mucormycosis, revealing its potential in treating neglected tropical diseases (Gebremariam et al., 2020).

Phase 1 studies on safety and pharmacokinetics evaluated oral and intravenous doses of Fosmanogepix in healthy participants, which showed linearity and proportionality in plasma exposure, with good tolerability and a half-life of approximately 2.5 days, without exhibiting toxicity. The adverse events were generally mild (Hodges et al., 2017). In phase 1b, a study in patients with neutropenic acute myeloid leukemia undergoing chemotherapy showed good tolerability for Fosmanogepix, with mild adverse events such as nausea and increased alanine aminotransferase. No serious adverse events led to discontinuation of the treatment (Cornely et al., 2023). Two studies evaluated the efficacy and safety of Fosmanogepix in patients with candidaemia. The first, in patients with common candidaemia, demonstrated a success rate of 80 % and a survival rate of 85 % were reported (Pappas et al., 2023), and in candidaemia caused by *C. auris*, showed a success rate of 89 % and good tolerability of the treatment were reported (Vazquez et al., 2023).

3.3.2. Ibrexafungerp

Ibrexafungerp, a next-generation triazole class antifungal that works by inhibiting the synthesis of an essential component of the fungal cell wall, (1–3)-β-D-glucan synthase, disrups the fungal cell wall, leading to fungal death (Apgar et al., 2021; Azie et al., 2020; Ghannoum et al., 2020) (Fig. 3). Ibrexafungerp has good tolerability and a favorable pharmacokinetic profile, including high oral bioavailability and a prolonged half-life, making it suitable for both intravenous and oral administration (Wring et al., 2017).

Ibrexafungerp exhibits a broad antifungal spectrum of activity, demonstrating efficacy against various pathogenic fungi, including those resistant to conventional treatments (Aldejohann et al., 2024). Ibrexafungerp has shown potent activity against several *Candida* species, including *C. glabrata* and different clades of *C. auris* (Azie et al., 2020; Ghannoum et al., 2020). Furthermore, ibrexafungerp retains *in vitro* activity against echinocandin-resistant strains of *C. glabrata* (Aldejohann et al., 2024). In addition, ibrexafungerp has shown antibiofilm properties against *Candida* species, including *C. auris* and *C. glabrata* (Marcos-Zambrano et al., 2017; Nunnally et al., 2019).

Ibrexafungerp has also demonstrated strong activity against several *Aspergillus* species, including azole-resistant strains (Ghannoum et al., 2018; Jiménez-Ortigosa et al., 2014; Pfaller et al., 2013). Its activity against Mucorales and *Fusarium* is limited, although it remains effective against other fungi, such as *Alternaria* and *Cladosporium* (Angulo et al., 2022; Lamoth and Alexander, 2015). *In vivo*, ibrexafungerp significantly reduced fungal burden in the kidneys in infections caused by *Candida* and *Aspergillus*, including resistant strains (Ghannoum et al., 2018; Petraitis et al., 2020; Wring et al., 2017). When combined with other antifungals, such as isavuconazole, it has synergistic effects, improving survival and reducing pulmonary damage in models of invasive aspergillosis (Petraitis et al., 2020). Ibrexafungerp also exhibits activity against ascus forms of *Pneumocystis*, controlling colonization and infection without complete eradication, which may be valuable in treating severe pulmonary infections (Borroto-Esoda et al., 2020).

Phase 2 and 3 studies have demonstrated the safety and efficacy of Ibrexafungerp for the treatment of invasive candidiasis. The use of oral Ibrexafungerp (1000 mg loading dose, followed by daily doses of 500 mg and loading doses of 1250 mg, followed by daily doses of 750 mg) after initial therapy with echinocandin was compared with treatment using an 800 mg loading dose of fluconazole, followed by daily doses of 400 mg; or daily intravenous doses of 100 mg of micafungin for fluconazole-resistant isolates. The results were similar across treatments, showing efficacy comparable to that of currently used antifungals (Spec et al., 2019). In a recent clinical study (NCT03059992), patients diagnosed with invasive candidiasis with documented evidence of failure, intolerance, or reported toxicity to standard antifungal treatment were treated with Ibrexafungerp, and the results revealed a favorable therapeutic response in the majority of patients with difficult-to-treat *Candida* spp. infections, including those caused by non-albicans *Candida* species (Alexander et al., 2020). A phase 3 study (NCT03363841) evaluated the efficacy of oral Ibrexafungerp in treating patients with invasive candidiasis or candidaemia caused by *C. auris*, and the results demonstrated significant efficacy, with 80 % of patients responding to the treatment, highlighting the importance of this new drug for treating infections caused by *C. auris* (Siebert et al., 2022). A phase 2 study of the use of Ibrexafungerp in the treatment of vulvovaginal candidiasis reported an efficacy rate of 78 %, whereas patients treated with fluconazole reported an efficacy of 66 % (Helou and Angulo, 2017).

3.3.3. Rezafungin

Rezafungin is a new antifungal agent belonging to the echinocandin class that acts by inhibiting (1→3)-β-D-glucan synthesis (Jacobs et al., 2022; Sofjan et al., 2018) (Fig. 3). Unlike conventional echinocandins, which require daily administration, rezafungin has a longer half-life, allowing weekly doses (Krishnan et al., 2017). This characteristic offers a significant advantage in terms of convenience and treatment adherence, especially in hospital settings and for patients undergoing prolonged therapy (Jacobs et al., 2022; Wiederhold et al., 2019b). Additionally, compared with other therapeutic options, rezafungin has shown a favorable safety profile, with minimal adverse events.

Like to other echinocandins, rezafungin has potent activity against *Candida* species, both azole-sensitive and azole-resistant (Pfaller et al., 2020; Tóth et al., 2019), and *in vivo* studies have shown that rezafungin has activity against *C. auris*, significantly reducing fungal burden and increasing survival rates in infected animals (Hager et al., 2018). Rezafungin also has activity against both azole-sensitive and azole-resistant species of *Aspergillus* (Nathan P Wiederhold et al., 2018a), exhibiting *in vivo* activity in a mouse model of azole-resistant disseminated invasive aspergillosis (Wiederhold et al., 2019b). Rezafungin is also active against some dermatophyte species, such as *Trichphyton mentagrophytes, T. rubrum, Microsporum gypseum* and *Epidermophyton floccosum* (Hoenigl et al., 2021).

Rezafungin has shown favorable safety and efficacy profiles in several clinical studies. Phase I studies demonstrated that weekly doses of up to 400 mg were safe, with most adverse effects being mild and transient (NCT02516904 and NCT02551549) (Sandison et al., 2017). Phase II studies (NCT02734862) further validated its safety in treating candidaemia and invasive candidiasis, with common mild side effects including diarrhea and hypokalemia (Thompson et al., 2021).

Efficacy studies in phase II trials have indicated that rezafungin, particularly with a 400 mg/200 mg weekly dosing regimen, is effective for candidaemia and invasive candidiasis and has high cure rates and rapid clearance of infection compared with standard care with caspofungin (Thompson et al., 2021). However, a phase II trial in vulvovaginal candidiasis (VVC) revealed that topical formulations of rezafungin were less effective than fluconazole was, leading to the discontinuation of its topical development (Nyirjesy et al., 2019).

Ongoing phase III trials (ReSTORE, NCT03667690 and ReSPECT, NCT04368559) aimed to evaluate its use in invasive candidiasis treatment and as prophylaxis against invasive fungal diseases caused by *Candida* spp., *Aspergillus* spp., and *P. jirovecii*, in patients undergoing allogeneic blood and marrow transplantation (Hoenigl et al., 2021).

Fig. 3 illustrates the mechanisms of action of the new antifungal options mentioned above.

4. Innovative approaches to mycosis therapy: exploring new treatment strategies

Given the increasing prevalence of resistant fungal infections, the toxicity of current antifungal agents, and the limited number of therapeutic options available, there is an urgent need to develop new antifungal treatments (WHO, 2022). This review explores promising antifungal strategies, including drug repurposing, nanotechnology-based innovations, antifungal peptides, combination therapies, and immunotherapy.

4.1. Drug repurposing strategies

Drug repurposing finds new applications for existing drugs improving the discovery and development of antifungal treatments with a novel fungal-specific mode of action, good selectivity and low toxicity (Kulkarni et al., 2023; Xue et al., 2018). Various drug classes, such as antibacterial, immunosuppressant, statin, antipsychotic, antidepressant, antiarrhythmic and antiviral drugs, exhibit antifungal activity with potential for clinical application (Zhang et al., 2021).

Screening compound libraries has identified potential antifungal candidates for drug repositioning (Barbarossa et al., 2022; dos Reis et al., 2021a).

In an effort to identify potential antifungal candidates against *A. fumigatus*, dos Reis et al. (2021a) screened 1127 compounds from two distinct drug collections. Ten effective drugs from various classes that exhibit either fungicidal or fungistatic properties with the potential to target specific cellular components were identified, as detailed in Table 1. Among them, miltefosine, an antiprotozoal, bactericidal, and antifungal agent, that seems to affect the sphingolipid biosynthesis pathway in *A. fumigatus*, has emerged as a promising candidate (dos Reis et al., 2021a).

In a subsequent screening with 1402 compounds against *A. fumigatus*, brilacidin emerged as the most prominent compound (dos Reis et al., 2023). Brilacidin, a drug that mimics host defense peptides, has been repurposed for use against several major human fungal pathogens, including *A. fumigatus, C. neoformans, C. albicans, C. auris, Rhizopus oryzae, Rhizopus delemar, Lichtheimia corymbifera, Mucor circineloides, Scedosporium apiospermum, Fusarium species, Mucor species, Sporothrix brasiliensis, Sporothrix schenckii* and *Rhizopus* species (Table 1) (Diehl et al., 2024; dos Reis et al., 2023; Larwood and Stevens, 2024). In yeast cells, brilacidin disrupts the membrane, alters cell wall integrity, and affects calcium metabolism (Diehl et al., 2024). In murine models of corneal infections caused by *A. fumigatus*, brilacidin reduced the fungal burden. In addition, brilacidin acts synergistically when combined with caspofungin and voriconazole against *A. fumigatus* (dos Reis et al., 2023); in the same way, the synergistic interaction of brilacidin with the new antifungal drug ibrexafungerp was described by Dos Reis et al. (2024) (Table 1).

Following the repositioning strategy, the compound collection called the "Pandemic Response Box", with 400 different compounds coming from the Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseasesm, was screened against *C. neoformans, C. deuterogattii* and *C. auris*. The antifungal activity was detected for five compounds, MMV1633966, MMV019724, MMV1593541, MMV565773, and MMV1593537 (Table 1), with the latter exhibiting the greatest potential. MMV1593537 presented fungicidal activity, promoted cell wall defects, reduced capsule size and increased the chitinase activity, likely through chitin enzymatic hydrolysis (de Oliveira et al., 2022).

Protease inhibitors (PIs) used for HIV treatment also demonstrated antifungal activity and potential for repurposing. HIV PIs reduce the levels of secreted aspartic proteases (Saps), a key virulence factors (Gruber et al., 1999). In addition, PIs also affect the lipid synthesis, biofilm formation, and the adhesion to epithelial cells and endocytosis, followed by promising responses for the control of *in vivo* infections in both immunocompetent and immunosuppressed mice (Palmeira et al., 2018b, 2008; Fenley et al., 2022). Indinavir has potential for inhibiting fungal pathogens such as *C. albicans, C. neoformans, A. fumigatus, Histoplasma capsulatum* var. *capsulatum* and *Fonsecaea pedrosoi* (Blasi et al., 2004a; Brilhante et al., 2016; dos Reis et al., 2021a; Gruber et al., 1999; Palmeira et al., 2018b). The other five HIV PIs, ritonavir, atazanavir, saquinavir, lopinavir, and nelfinavir, exhibited synergistic activity with AmB against *C. neoforamans* and *C. gattii*, suggesting a potential strategy to reduce de AmB doses and the treatment costs (Alkashef and Seleem, 2024).

Furthermore, atazanavir and saquinavir showed synergistic activity with azoles in the control of the multidrug-resistant pathogen *C. auris*, as shown in Table 1 (Elgammal et al., 2023a, 2023b). The combinations with posaconazole and ritonavir, almost completely reduced the *C. auris* burden in the kidneys of infected mice. The combination of atazanavir and saquinavir with posaconazole also demonstrated anti-*C. auris* biofilm activity, reducing biofilm formation by 66 % compared with that of the untreated control (Elgammal et al., 2024). These combinations were also effective against *C. albicans, C. tropicalis, C. parapsilosis, C. krusei* and *C. glabrata*, which are among the most clinically important pathogens of *Candida* species (Cordeiro et al., 2017; Lohse et al., 2020; Santos et al.,

Table 1
Advances in drug repositioning against pathogenic fungi.

Drug	Fungi	MIC	*In vivo*	Mode of action	Drug in combination	Reference
3-bromopyruvate (3BP)	*C. albicans* *C. glabrata* *C. tropicalis*	256 μg/mL	Yes, mouse model	Unknow	Unknow	(Jothi et al., 2023)
5-Fluorouracil	*C. albicans*	0.25–1 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Albendazole	*F. pedrosoi* *C. neoformans* *A. fumigatus* *A. flavus* *A. terreus* *A.nidulans* *A. niger*	1.25 μM 5 μM 0.03–1 mg/L	No	Unknow	Unknow	(Berthet, 2003; Coelho et al., 2023; Sutar et al., 2021)
Atazanavir	*C. neoformans* *C. gattii* *C. auris* C. albicans *C. tropicalis* *C. parapsilosis* *C.* krusei *C. glabrata*	16 μg/mL >128 μg/mL	Yes, *C. elegans* and murine model	Sap hydrolytic activity	AmB (0.0625 μg/mL). Posaconazole (3 mg/Kg) Itraconazole (5 mg/Kg)	(Alkashef and Seleem, 2024; Elgammal et al., 2024)
Bleomycin	*C. albicans*	1–4 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Bleomycin	*S. cerevisiae* *C. neoformans* *Candida* spp. *A. fumigatus*	3.2 μg/mL 6.4 μg/mL 0.39–12.5 μg/mL 3.2 μg/mL	No	Unknow	Unknow	(Graybill et al., 1996; Moore et al., 2003;Pokharel et al., 2022)
Brilacidin	*A. fumigatus* *C. neoformansC. albicansC. aurisL. corymbiferaMucor circineloidesS. apiospermumFusarium speciesMucor speciesSporothrix brasiliensisSporothrix schenckiiRhizopus species*	>80 μM 2.5 μM 80 μM 8 μM 16 μM 8 μg/mL 16–64 μg/mL 32–64 μg/mL 64 μg/mL 16–32 μg/mL 32–64 μg/mL	Yes, murine model	Unknow	Caspofungin 0.2 or 0.5 μg/mL) Voriconazole (0.125 -0.25 μg/mL)	(Dos Reis et al., 2024; dos Reis et al., 2023; Larwood and Stevens, 2024)
Carboplatin	*C. albicans*	0.5–1 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Cisapride	*A. fumigatus*	1.56 μM	No	Parasympathomimetic acting as a serotonin 5-HT4 agonist.	Unknow	(dos Reis et al., 2021b; Orihata and Sarna, 1994)
Cisplatin	*C. albicans*	0.5–1 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Darunavir	*C.* albicans	512 μg/mL	Yes, *G. mellonella*	Sap hydrolytic activity	Unknow	(Fenley et al., 2022)
Decarbazine	*C. albicans*	0.25–1 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Docetaxel	*C. albicans*	2–4 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Doxorubicin	*C. albicans*	1 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Econazole nitrate	*A. fumigatus*	12.5 μM	No	Inhibits ergosterol synthesis	Unknow	(dos Reis et al., 2021b; Heel et al., 1979)
Enalaprilat	*A. fumigatus*	25 μM	No	Angiotensin-converting enzyme inhibitor	Unknow	(Davies et al., 1984; dos Reis et al., 2021b)
Etoposide	*C. albicans*	1–4 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Fenbendazole	*C. neoformansC. Gattii*	0.012 g/ml	Yes, murine model	Affects-tubulin distribution and protein kinases	AmB 0.0625–0.2500 μg/ml	(de Oliveira et al., 2024, 2020)
Fluoxetine	*Candida* spp	40–160 μg/mL	No	Unknow	Unknow	(Costa Silva et al., 2017)

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Table 1 (*continued*)

Drug	Fungi	MIC	*In vivo*	Mode of action	Drug in combination	Reference
Fluvastatin	*A. fumigatus*	25 μM	No	Blocks ergosterol biosynthesis by inhibition of farnesyl pyrophosphate production	Unknow	(dos Reis et al., 2021b; Tavakkoli et al., 2020)
Gemcitabine	*C. albicans*	2–4 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Indinavir	*F. pedrosoi*		No	Unknow	Unknow	(Palmeira et al., 2018a)
Indinavir sulphate	*A. fumigatus* *C. albicans* *C. neoformans* *F. pedrosoi*	6.25–10 μM	No	Protease inhibitor	Unknow	(Blasi et al., 2004b; dos Reis et al., 2021b; Gruber et al., 1999; Palmeira et al., 2018a)
Iodoquinol	*A. fumigatus*	2 μM	No	Unknow	Unknow	(dos Reis et al., 2021b; Gupta et al., 2004)
Irinotecan	*C. albicans*	1 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Leucovorin or folinic acid	*C. albicans*	1 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Lopinavir	*C. albicans* *C. neoformans* *C. gattii*	IC50 = 39.8 μM 16 μg/mL	Yes, murine and *C. elegans* model.	Inhibited the Sap hydrolytic activity.	Fluconazole (10 mg/mL) AmB (0.0625 μg/mL)	(Alkashef and Seleem, 2024; Santos et al., 2021)
Mesoridazine	*A. fumigatus*	3.12 μM	No	Unknow	Unknow	(dos Reis et al., 2021b; Su, 2004)
Miltefosine	*A. fumigatus*	10 μM	No	Possibly interferes with sphingolipid biosynthesis.	Unknow	(dos Reis et al., 2021b; Roatt et al., 2020)
MMV565773	*C. neoformans* *C. gattii* *C. auris*	2,5–10 μM	No	Unknow	Unknow	(de Oliveira et al., 2022)
MMV019724	*C. neoformans* *C. gattii* *C. auris*	2,5–5 μM	No	Unknow	Unknow	(de Oliveira et al., 2022)
MMV1593537	*C. neoformans* *C. gattii* *C. auris*	5 μM 5 μM 5M	No	Seems associated with chitinase activity	Unknow	(de Oliveira et al., 2022)
MMV1593541	*C. neoformans* *C. gattii* *C. auris*	10 μM	No	Unknow	Unknow	(de Oliveira et al., 2022)
MMV1633966	*C. neoformans* *C. gattii* *C. auris*	2,5–5 μM	No	Unknow	Unknow	(de Oliveira et al., 2022)
Nelfinavir	*C. neoformans* *C. gattii* *F. pedrosoi*	16 μg/mL	*C. elegans* - AmB (0.125 μg/mL) combined with nelfinavir (8 μg/mL)- reduce fungal load.	Sap hydrolytic activity	AmB (0.0625 μg/mL)	(Alkashef and Seleem, 2024; Palmeira et al., 2018a)
Oxaliplatin	*C. albicans*	1–2 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Oxiconazole nitrate	*A. fumigatus*	25 μM	No	Inhibits ergosterol biosynthesis.	Unknow	(Del Rosso and Kircik, 2013; dos Reis et al., 2021b)
Paclitaxe	*C. albicans*	2 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Paroxetine	*Candida* spp	10–15.9 μg/mL	No	Unknow	Unknow	(Costa Silva et al., 2017)
Ritonavir	*C. neoformans* *C. gattii* *H. capsulatum* *F. pedrosoi*	16 μg/mL 0.0312 to 4 μg mL/mL and from 0.0625 to 1 μg mg/mL for ritonavir in filamentous and yeast phase 100 μM	Yes, *C. elegans* model	Sap hydrolytic activity	AmB (0.0625 μg/mL) Itraconazole	(Alkashef and Seleem, 2024; Brilhante et al., 2016; Palmeira et al., 2018a)
Saquinavir	*C. neoformans* *C. gattii* *C. auris*	16 μg/mL >128 μg/mL 512 μg/mL	Yes, murine and G. mellonella models	Sap hydrolytic activity	AmB (0.0625 μg/mL) Posaconazole (3	(Alkashef and Seleem, 2024; Brilhante et al., 2016; Elgammal et al., 2024,

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Table 1 (*continued*)

Drug	Fungi	MIC	*In vivo*	Mode of action	Drug in combination	Reference
	C. albicans	0.125–1 μg /mL			mg/kg)	2023a; Fenley et al., 2022; Palmeira
	C. tropicalis	100 μM			Itraconazole (5	et al., 2018a)
	C. parapsilosis				mg/kg)	
	C. krusei					
	C. glabrata					
	H. capsulatum					
	F. pedrosoi					
Sertraline	*Candida* spp	40–100.8 μg/mL	Yes, murine model	Unknow	Amphotericin B	(Cong et al., 2016; Costa Silva et al.,
	T. asahii	4–8 μg/ml			(0.5 μg/mL)	2017; Lass-Florl, 2001; Paul et al.,
	Cryptococcus spp.	2–32 μg/mL			Caspofungin	2016; Villanueva-Lozano et al., 2019)
	Aspergillus species	3–237 mg/L			(4 μg/mL)	
	Sporothrix schenckii	4–8 μg/ml			Fluconazole (0.5	
	Coccidioides immitis	4–8 μg/ml			μg/mL)	
Tamoxifen	*C. albicans*	1–2 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Vinblastine	*C. albicans*	0.25–0.5 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Vincristine	*C. albicans*	0.25–1 mg/mL	No	Unknow	Unknow	(Wakharde et al., 2018)
Vincristine sulfate	*A. fumigatus*	25 μM	No	Inhibits microtubule formation	Unknow	(dos Reis et al., 2021b; Franzyk and Christensen, 2021)
Haloperidol-Compound B10	*C. albicans*	16 μg/mL	Yes, murine model	Unknow	Unknow	(Ji et al., 2020)
	C. glabrata	4 μg/mL				
	C. neoformans	2 μg/mL				
Aripiprazole	*C. albicans*	>500 μg/mL	No	Unknow	Unknow	(Rajasekharan et al., 2019)

2021; Fenley et al., 2022; Elgammal et al., 2024). The efficient reduction in biofilm formation by HIV protease inhibitors has also been reported in previous studies involving *C albicans* and *Trichosporon* (Cordeiro et al., 2017; Lohse et al., 2020; Santos et al., 2021).

Antipsychotic drugs such as haloperidol and aripiprazole have shown potential in controlling fungal infections. Haloperidol, a butylbenzoic antipsychotic, along with its improved pharmacological derivative B10, can control candidiasis and cryptococcosis in both *in vitro* and *in vivo* models. B10 exhibited a synergistic response with fluconazole, controlling *C. albicans* infections in mice. Moreover, B10 dose-dependently inhibits biofilm formation in *C. neoformans* and *C. albicans* (Ji et al., 2020). Similarly, aripiprazole inhibits biofilm development in *C. albicans* (Rajasekharan et al., 2019). However, while it shows promising effects *in vitro*, it has not been confirmed as a viable option for *in vivo* treatment (Reitler et al., 2024).

Anthelmintic compounds, specifically benzimidazoles, have also been repurposed for use against fungal pathogens (Bansal et al., 2019). Among them, albendazole has been associated with the control of *F. pedrosoi* (Coelho et al., 2023), *C. neoformans* (Sutar et al., 2021), *A. fumigatus, Aspergillus flavus, Aspergillus terreus, A. nidulans* and *A. niger* (Berthet, 2003) (Table 1).

Fenbendazole, a benzimidazole, has demonstrated potent anti-cryptococcal activity and is a promising candidate for combating cryptococcosis, showing low toxicity to mammalian cells when tested alone or in combination with AmB (de Oliveira et al., 2020). Its mode of action against *Cryptococcus* involves the disruption of β-tubulin (de Oliveira et al., 2020), similar to its effect on helminth parasites (Lacey, 1988). Furthermore, fenbendazole treatment altered the abundance of protein kinases in *Cryptococcus*. Mutants lacking *Chk1, Tco2, Tco3, Bub1*, and *Sch9* presented increased resistance to fenbendazole, highlighting the role of these pathways in the antifungal response (de Oliveira et al., 2024). The combination of fenbendazole and AmB showed synergistic activity against *Cryptococcus*, with a broader concentration range (Table 1). Additionally, intranasal administration of fenbendazole effectively controlled cryptococcosis in mouse models (de Oliveira et al., 2020), reducing the fungal burden in the lungs to a similar extent as combination therapy with AmB (de Oliveira et al., 2024).

The repurposing of anticancer drugs is another promising antifungal alternative (Wakharde et al., 2018; Pokharel et al., 2022). Bleomycin, an antineoplastic agent that targets the phospholipid synthesis pathway downstream of phosphatidyl serine production, controls *S. cerevisiae, C. neoformans, Candida* spp., and *A. fumigatus* at low MIC concentrations (Graybill et al., 1996; Moore et al., 2003; Pokharel et al., 2022) (Table 1). Furthermore, the anticancer molecule 3-bromopyruvate (3BP) induced damage to yeast via loss of membrane integrity, nuclear condensation, and increased reactive oxygen species (ROS). In a vulvovaginal model (VVC), a vaginal cream with 3BP reduced the *C. albicans* burden and protected the vaginal membrane, highlighting its potential for candidiasis treatment (Jothi et al., 2023) (Table 1).

The antifungal activity of antidepressants, specifically serotonin reuptake inhibitors (SSRIs), has been investigated. Fluoxetine, sertraline, and paroxetine can control *Candida* species, effectively inhibiting both biofilm and planktonic cells (Costa Silva et al., 2017; Gowri et al., 2020). Among these, sertraline has emerged as the most promising candidate for repurposing, displaying antifungal activity not only against *Candida* species *e.g. C. auris* (Gowri et al., 2020) but also against *Aspergillus* species (Lass-Florl, 2001), *Coccidioides immitis* (Paul et al., 2016), *S. schenckii* (Villanueva-Lozano et al., 2019), *Cryptococcus* spp. (Breuer et al., 2022; Treviño-Rangel et al., 2016), and *Trichosporon asahii* (Cong et al., 2016) (Table 1). In murine models of cryptococcal infections, sertraline effectively controls fungal burdens in the brain and spleen, highlighting it as a putative alternative for the treatment of cryptococcosis (Treviño-Rangel et al., 2016). Sertraline's mode of action is linked to the induction of supersized lipid droplet formation, which likely affects lipid metabolism and causes extensive membrane damage (Breuer et al., 2022; da Silva et al., 2023).

Despite promising advances, most of the compounds listed here require further elucidation of their modes of action and *in vivo* efficacy before they can be effectively repositioned as antifungal treatments.

4.2. Nanotechnology-based strategies

Nanotechnology has emerged as a promising platform to enhance antifungal treatments by reducing toxicity, improving bioavailability, and enabling targeted delivery (Soliman, 2017; Zadeh Mehrizi et al., 2024). Organic or polymeric nanoparticles (NPs) are defined as structures with a diameter range of 1–1000 nm, whereas nanomaterials have a size range of 1–100 nm (Pinto Reis et al., 2006; Soliman, 2017). The best nanotechnology strategies include nanoemulsions, nanosuspensions, microneedles, metal-based NPs, polymeric NPs, lipid-based carriers and conjugates (Soliman, 2017; Zadeh Mehrizi et al., 2024).

Antifungal drugs often exhibit hydrophobic properties, which can limit their solubility and bioavailability (Soliman, 2017; Zadeh Mehrizi et al., 2024). Liposomal formulations of AmB (*e.g.*, AmBisome) represent a successful nanotechnology application that significantly reduce nephrotoxicity (Brüggemann et al., 2022; Maertens et al., 2022; Stone et al., 2016;Hiemenz and Walsh, 1996). Despite this progress, further complementary strategies are needed to enhance AmB formulations. To address these challenges, nanotechnology-based approaches have been explored, as recently reviewed by Mehrizi et al. (2024).

Synthetic polymers, such as poly(butyl cyanoacrylate) (PBCA), poly (lactic acid) (PLA), poly(lactide-co-glycolide) (PLGA), poly(ε-caprolactone) (PCL), and poly(alkylcyanoacrylates) (PACA), or natural polymers, such as chitosan, sodium alginate, and collagen, are commonly used in the formulation of nanospheres and nanocapsules. These nanomedicine approaches offer improved stability; can be administered via parenteral, oral, or topical routes; and can improve the stability and delivery of antifungal agents (Adel et al., 2023; Wang et al., 2014). Notably, compared with itraconazole alone, the PLGA nanospheres enhanced the efficacy of itraconazole treatment 100-fold (Patel et al., 2010). Similar enhancements were observed with voriconazole, clotrimazole and AmB (Ćurić et al., 2015; Martínez-Pérez et al., 2018; Peng et al., 2008; Tang et al., 2015; Xie et al., 2013). Interestingly, the combination of PLGA-NPs with clotrimazole was enhanced by chitosan NPs, increasing antifungal efficiency for vaginal applications (Martínez-Pérez et al., 2018). Other promising nanosystems, such as PBCA nanospheres and zein-NPs, are available for itraconazole delivery (Adel et al., 2023; Ćurić et al., 2017, 2015).

The antifungal potential of metal NPs, particularly with gold (AuNP) and silver nanoparticles (AgNPs), has been described. These NPs can be synthesized via both nonbiological (chemical, electrochemical, and photochemical reduction) and biological methods (Manjumeena et al., 2014; Sakthi Devi et al., 2022). AuNPs have demonstrated fungicidal activity *in vitro* against *Candida* species, *C. neoformans*, and *A. fumigatus*. *In vivo* studies have shown that AuNPs are effective against cutaneous candidiasis in mice (Abdallah and Ali, 2022; Ayad Kareem et al., 2021; da Silva et al., 2022; Rónavári et al., 2018).

However, AgNPs stand out for their increased antifungal activity (Lotfali et al., 2021). AgNPs disrupt fungal cell membranes by creating pores, effectively inhibiting the growth of pathogens such as *C. albicans, C. glabrata, C. krusei, C. tropicalis, Fusarium* species, *Aspergillus* species, mucormycosis, and dermatophytes such as *Microsporum* and *Trichophyton* (Chatterjee et al., 2022; Hashem et al., 2022; Mallmann et al., 2015; Manjumeena et al., 2014; Matras et al., 2022; Rónavári et al., 2018). Furthermore, AgNPs have emerged as a viable alternative for overcoming fluconazole resistance in *Candida* species, as they also inhibit virulence factors (Artunduaga Bonilla et al., 2015; Bharti et al., 2024; Miškovská et al., 2022; Paulo et al., 2024).

Therefore, NP formulations can be used to enhance antifungal treatment or serve as novel antifungal therapies. However, addressing regulatory issues and standardizing *in vitro* and *in vivo* characterization methods will be crucial to make the transfer of NP formulations from research laboratories to the pharmaceutical industry possible.

4.3. Antifungal peptides

Antifungal peptides (AFPs) represent a promising therapeutic strategy because of their ability to target multiple fungal structures and pathways, including cell walls, RNA, DNA, and cell cycle proteins (Fernández de Ullivarri et al., 2020). These bioactive molecules are categorized based on the basis of their origin: synthetic, semisynthetic, or natural. Natural AFPs are produced by various biological systems, including bacteria, yeast, plants, and animals, as part of their evolutionary defense responses (De Lucca and Walsh, 1999; Fernández de Ullivarri et al., 2020). Regardless of their source, AFPs are small amino acid chains, with fewer amino acids correlated with increased stability, reduced toxicity, and lower production costs (Duncan and O'Neil, 2013).

Many AFPs are cataloged in large databases, similar to previous reports on drug repositioning. Two major collections are the Antimicrobial Peptide Database (APD) (Wang et al., 2016, 2009; Wang, 2004), which includes 3940 peptides, 1495 with antifungal activity (available in https://aps.unmc.edu/database/anti; accessed on October 2, 2024), and the Collection of Anti-Microbial Peptides (CAMP) (Waghu et al., 2016; Waghu and Idicula-Thomas, 2020), which contains 24,243 sequences, including 4783 with antifungal properties (available in http://www.camp3.bicnirrh.res.in/index.php; accessed on October 2, 2024). These databases include details on peptide origin, research status, antifungal spectrum, and potential targets or modes of action.

These resources support AFPs research against different pathogenic fungi, as shown in a recent screening of AFPs from the APD (Lai et al., 2024). This study was based on structural and functional parameters and revealed a strong correlation between antifungal activity and the positive net charge and hydrophobicity of these peptides. Among the peptides tested, IR3 stood out for its stability against proteases, salts, and serum, along with low cytotoxicity. IR3 exhibited the most potent antifungal activity against *C. albicans* both *in vitro* and *in vivo*, acting through multiple mechanisms, including biofilm eradication, the induction of reactive oxygen species (ROS), and membrane disruption. Given its multifaceted antifungal action and strong efficacy, IR3 presents a promising alternative for the treatment of fungal infections (Lai et al., 2024).

In this context, we highlight several specific promising AFPs reported in recent years. Novel natural antifungal peptides have shown potential in controlling the growth of *Aspergillus* species (Muhialdin et al., 2015; Pimienta et al., 2022), *Candida* species (Freitas and Felipe, 2023; Guilhelmelli et al., 2016), and *C. neoformans* (Guilhelmelli et al., 2016) —some of the most prevalent fungal pathogens. For example, natural bioactive peptides such as the salivary proteins histatin 5 and statherin have demonstrated antifungal activity, particularly against *C. albicans*, by inhibiting its colonization of epithelial surfaces and reducing biofilm biomass. These peptides are an alternative for synergistic therapies for *Candida*-related infections (Moffa et al., 2015; Pellissari et al., 2021; van 't Hof et al., 2014; Vukosavljevic et al., 2012; Williams et al., 2013).

Synthetic peptides such as PepGAT and PepKAA also demonstrated antibiofilm activity against *Candida* species. When combined with nystatin or itraconazole, these peptides synergistically reduce biofilms while resulting in lower drug toxicity in red blood cells (Bezerra et al., 2022). Additionally, synthetic lipo-γ-AA peptides, a class of peptidomimetics, exhibit potent antifungal activity against *C. albicans*, non-*albicans Candida* species, and other pathogens such as *C. neoformans, C. gattii, Mucor racemosus*, and *A. fumigatus*. Their machinery functions primarily by disrupting fungal cell membranes (Zhang et al., 2022).

Despite significant advances in AFP research, particularly with the establishment of comprehensive databases, several open questions remain open. There is a need to evaluate these molecules against major fungal pathogens and to elucidate their modes of action to fully understand their therapeutic potential.

4.4. Antifungal combination therapy

Antifungal combination therapy has emerged as a promising alternative to traditional monotherapy, as it targets more than one fungal structure, reducing resistance rates (Lignieres et al., 2022; Martin-Pena et al., 2014; Neoh and Slavin, 2024). Some studies have demonstrated the efficacy of antifungal combinations, which have has been conducted using both *in vitro* and *in vivo* models. For instance, combinations of azoles with echinocandins—such as caspofungin or anidulafungin with voriconazole (Calvo et al., 2012; MacCallum et al., 2005; Petraitis et al., 2009)—and itraconazole or isavuconazole with micafungin have shown increased survival rates compared to monotherapy (Clemons, 2006; Clemons et al., 2005; Luque et al., 2003; Petraitis et al., 2017).

Caspofungin, one of the first options for treating candidaemia, exhibits synergistic activity against *Candida* species when combined with major antifungal drugs such as azoles, polyenes (*e.g.*, AmB), 5-fluorocytosine, and allylamines (Su et al., 2022). In humans, the combination of caspofungin and voriconazole was effective in 90 % of patients, achieving a 100-day survival rate of 86.3 % (Lee et al., 2017).

The combination of terbinafine and itraconazole has been shown to be effective against *Fonsecaea, C. albicans, Aspergillus* and *Scedosporium* (Cuenca-Estrella, 2004; Gupta et al., 2002; Zhang et al., 2009). This combination has also been identified as an efficient strategy for treating dermatophytosis (Ramzi et al., 2023; Sharma et al., 2020; D. Zhang et al., 2021).

In murine models of pulmonary mucormycosis, the combination of L-AmB and isavuconazonium sulfate was more effective than monotherapy, reducing the tissue fungal burden and prolonging survival, indicating its potential as an alternative therapy for human mucormycosis (Gebremariam et al., 2021). Interestingly, guidelines from the Infectious Diseases Society of America (IDSA) and the World Health Organization (WHO) recommended the combination of AmB and flucytosine as the first-line therapy for cryptococcosis and cryptococcal meningitis. This combination has demonstrated a strong fungicidal effect on *Cryptococcus* infections, achieving therapeutic responses with lower doses in a shorter time (Maziarz and Perfect, 2016; Perfect and Bicanic, 2015; Spitzer et al., 2017).

4.5. Immunotherapy

Despite significant efforts to develop antifungal vaccines, no approved formulations are currently available (Boniche et al., 2020; Rudkin et al., 2018). Promising antifungal immunotherapies, including both therapeutic and prophylactic protocols, are being explored to control the progression of fungal infections and prevent their dissemination (Boniche et al., 2020; Chechi et al., 2023; Levitz, 2017; Posch et al., 2017). Studies analyzing fungal secretomes and proteomes are important in selecting antigens for vaccine development. Additionally, vaccination strategies using avirulent strains, polymicrobial formulations, nanoparticles, and extracellular vesicles (EVs) are under investigation. These approaches have identified potential immunogenic candidates against major fungal pathogens, including *Aspergillus* spp., *Candida* spp., *Coccidioides* spp., *Cryptococcus* spp., *Paracoccidioides* spp., *Sporothrix* spp., *Histoplasma* spp., *Pneumocystis jirovecii*, and molds of the order *Mucorales*. Several immunomodulatory strategies have shown promising effects by inducing rapid antibody production, reducing fungal burden, and altering cytokine responses. However, even the most advanced studies remain in the preclinical stages (Akhtar et al., 2023; Araújo et al., 2020; B R Da Silva et al., 2020; de Almeida et al., 2018; Eddens et al., 2019; Edwards et al., 2018; Hayden et al., 2019; Kamli et al., 2022; Khan et al., 2022; Rabacal et al., 2022; Singh et al., 2022; Tabassum et al., 2022; Ueno et al., 2020).

5. Conclusion

The current arsenal we rely on to combat fungal infections is no longer sufficient. Polyenes, pyrimidine analogs, azoles, and echinocandins, which are currently used in clinical practice, face serious challenges due to increasing resistance, high toxicity potential, and their association with costly treatments. This situation severely impacts public health systems that cannot ensure treatment, especially in regions heavily affected by fungal infections, leading to an alarming number of deaths associated with these diseases.

Efforts are being made to address the problem and mitigate the issues associated with fungal infections. Clinical studies are currently underway to test the efficacy and safety of new antifungal drugs that may substantially contribute to reversing the current reality. These new drugs target nucleic acid metabolism (olorofim), the fungal cell membrane (oteseconazole, VT-1598, opelconazole, and encapsulated AmB), and the fungal cell wall (fosmanogepix, ibrexafungerp, and rezafungin). Among them, olorofim is already recommended by the FDA for the treatment of invasive infections caused by filamentous fungi and central nervous system infections caused by the fungus *Coccidioides* spp. in patients who do not respond to conventional treatments, demonstrating the potential impact these new drugs may have on fungal infection control.

Despite these advances, the problem is far from being resolved. Therefore, researchers worldwide are seeking new antifungal alternatives that combine efficacy and safety using various strategies such as drug repurposing, nanotechnology-based innovations, antifungal peptides, combination therapies, and immunotherapy. All these efforts contribute to addressing this major public health issue we face, with the potential to save millions of lives annually across the globe.

Credit authorship contribution statement

Cássia Milena de Souza: Writing - Original Draft, Writing - Review & Editing, Visualization. Bárbara Tavares Bezerra: Writing - Original Draft, Writing - Review & Editing, Visualization. Daniel Agreda Mellon: Writing - Original Draft, Writing - Review & Editing, Visualization. Haroldo Cesar de Oliveira: Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Conceptualization.

Declaration of competing interest

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

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT 4o mini (Open IA - https://chatgpt.com/) in order to improve the grammatical quality of the English language, which is not the native language of the authors, used to write this review. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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