Published in final edited form as:

Expert Opin Pharmacother. 2021 May ; 22(7): 867–887. doi:10.1080/14656566.2021.1873951.

CURRENT AND PROMISING PHARMACOTHERAPEUTIC OPTIONS FOR CANDIDIASIS

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Abstract

Introduction: *Candida* spp. are commensal yeasts capable of causing a wide range of infections such as superficial, oral, vaginal, or even systemic infections. Despite medical advances, the antifungal pharmacopeia remains limited and the development of alternative strategies is needed.

Areas covered: The authors discuss available treatments for *Candida* spp. infections, highlighting advantages and limitations related to pharmacokinetics, cytotoxicity, and antimicrobial resistance. Moreover, they present new perspectives to improve the activity of the available antifungals, discussing their immunomodulatory potential and advances on drug delivery carriers. Several new therapeutic approaches are presented including recent synthesized antifungal compounds; drug repurposing using a diversity of antibacterial, antiviral and non-antimicrobial drugs; combination therapies with different compounds or photodynamic therapy; and finally innovations based on nano-particulate delivery systems.

Expert opinion: With the lack of novel drugs, the available assets must be leveraged to their best advantage through modifications that enhance delivery, efficacy, and solubility. However, these efforts are met with continuous challenges presented by microbes in their infinite plight to resist and survive therapeutic drugs. The pharmacotherapeutic options in development need to focus on new antimicrobial targets. The success of each antimicrobial agent brings strategic insights to the next phased approach in treating *Candida* spp. infections.

Keywords

Candida spp.; antifungal compounds; drug repurposing; drug combination; drug delivery

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Declaration of Interest:

E Mylonakis participates in the Cidara_ ReSTORE multicenter trial and in the past has received grant support from Synexis, Sanofi, T2 Biosystems and Astellas. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures:

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

1 Introduction

Systemic *Candida* spp. infections present a significant challenge to the medical community. Infections are difficult to diagnose, treat, and sometimes can relapse as persistent infections [1,2]. As part of the natural microbiome, *Candida* spp. are commensal yeasts found in the skin, oral cavity, and gut microbiota [3]. However, impaired host immune responses or tissue trauma can lead to dysbiosis and allow commensal yeast to transition into opportunistic pathogens [4,5]. Pathogenic *Candida* spp. can exhibit several virulence factors such as adhesins, morphological switching (transitioning from yeast cells to filamentous forms), secretion enzymes (proteases and phospholipases), and biofilms [4,5]. Many studies reported that *Candida* biofilms can be formed on the mucosa, skin or medical devices surfaces, and lead to oral, vulvovaginal, wound or systemic infections [6–8]. The ability of *Candida* spp. to form biofilms results in several clinical implications since the biofilm structure protects *Candida* cells from host immune system and antifungal drugs [6–8]. Although the biofilm formation on abiotic surfaces and its role in systemic candidiasis is already established, the formation of *Candida* biofilms on mucosa surfaces remains questionable [9,10]. Previous studies demonstrated that *C. albicans* form biofilms *in vivo* on mucosa surfaces in animal models of oral [11] and vulvovaginal candidiasis [12], however Swidsinski *et al.* [10] did not find biofilms on vaginal biopsies of patients with candidiasis.

Patients at risk for invasive candidiasis are those experiencing prolonged care in intensive care units, patients receiving abdominal surgery, individuals suffering from acute necrotizing pancreatitis, hematologic malignant disease, solid-organ transplantation, solid-organ tumors, patients receiving hemodialysis, low birth weight or preterm infants, recipients of broad-spectrum antibiotics, glucocorticoids, or anti-cancer chemotherapy, patients with central vascular catheter and/or total parenteral nutrition, and individuals with advanced acquired immunodeficiency syndrome (AIDS) [3,13,14]. Thus, there is a significant vulnerable patient population at risk for infection. This diverse population can add to the difficulty of recognizing infections. Further, the spectrum of medications required to treat underlying diseases or conditions within this populations can also present a challenge in effectively treating fungal infection.

The arduous task to effectively diagnose and treat fungal infections within the vulnerable population is further made difficult by the variance of medically significant candidiasis causing species. *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei* are the most frequent pathogens of candidiasis with differing patterns of epidemiology and antifungal susceptibility [3,15]. Although the infections by non-*albicans Candida* species have significantly increased, *C. albicans* remains the most prevalent and pathogenic species [16,17]. Recently, a new species has been detected worldwide, *Candida auris*, and has garnered concern due to antifungal resistance profiles [18].

The treatment of candidiasis is restricted by the limited therapeutic arsenal, high cost, and narrow antifungal drug spectrum of action [19]. Another obstacle is the toxicity profiles from certain available therapeutics due to the similarity between eukaryotic fungal and

human cells [20], manifesting as nephrotoxicity and hepatotoxicity. Some drug regimens require hospitalization to monitor for these toxic effects and can require mediation through adjusted dosages, limited use, or eventually discontinuation of therapy [21]. Effective treatment is also hampered by global emergence of resistance (Table 1). Developed resistance puts tension on an already limited drug arsenal. Drug failure can also occur when medications for primary ailments antagonize antifungal agents, creating a maelstrom [22].

In this review, we discuss current available treatments licensed for monotherapy against *Candida* spp. infections (polyenes, azoles, and echinocandins), highlighting advantages and limitations. Additionally, we address potential new therapeutic strategies to provide perspectives for future management of superficial and invasive candidiasis.

2 Current available treatments

2.1 Polyenes

Polyene drugs are very effective at inhibiting *Candida* spp. and a multitude of other fungal pathogens. Inhibition is enabled through targeting ergosterol, a cholesterol-like substance in the fungal cell membrane, a structure important for maintaining cell integrity [23,24]. Until now, it was postulated that polyenes lead to ergosterol disruption by forming small channels in the fungal membrane and, consequently, promoting leakage of intracellular ions [20,25]. However, recent studies have shown that polyenes also form large extra-membranous aggregates that extract ergosterol from cell membrane lipid bilayers like a sterol sponge [26–28]. Therefore, the polyenes mechanism of action could be primarily attributed to ergosterol removal [26–28]. Polyenes also damage the fungal cell by forming reactive oxygen species (ROS) and by inhibiting the membrane transporters of some amino acids and glucose [29]. The commonly used polyenes for *Candida* spp. treatment are amphotericin B (AmB) and nystatin.

2.1.1 Amphotericin B—AmB is poorly absorbed in the gastrointestinal tract and parenteral administration is required. Despite its high efficiency, this antifungal causes serious collateral damage including nephrotoxicity, anaphylaxis, and electrolyte abnormalities [30,31]. Side effects can be explained by poor solubility in water and aggregate formation, which are also able to extract cholesterol from mammalian cells causing toxicity [30,32]. Due to low aqueous solubility, AmB needs to be ensconced by a carrier agent, resulting in different pharmaceutical formulations. Commercially available AmB formulations are Fungizone® (original formulation with sodium deoxycholate), Abelcet® (lipid complex formulation), Amphocil® (colloidal dispersion formulation), and AmBisome® (liposomal formulation), all administrated intravenously.

Over the years, many studies have been performed to compare the efficacy and safety of these different formulations. Recently, Steimbach *et al.* [33] evaluated the treatments with AmB deoxycholate and lipid-based AmB formulations in a systematic review including randomized controlled trials in patients with any degree of immunosuppression and susceptibility to invasive fungal infection. Analyzing several studies performed in the U.S. (9), France (4) and India (3), the authors found that AmB deoxycholate presented the same efficacy of the lipid-based AmB formulations. However, lipid-based formulations showed a

safer profile with reductions in adverse effects, including nephrotoxicity, fever, chills, and vomiting.

Despite the lack of oral formulations and adverse effects, AmB continues to be widely used due to its broad spectrum fungicidal activity against yeasts, molds, and dimorphic fungi [34]. Despite the extensive use of polyenes over the past 50 years, the emergence of *Candida* spp. resistance to this antifungal class is uncommon, possibly because removal of ergosterol alters all cellular processes dependent on membrane ergosterol and simultaneous mutations at these targets are highly improbable [26,28,33–35]. Although resistance is rare, Bailly *et al*. documented increasing MIC values of *C. glabrata* strains from patients under AmB treatment, and suggested that reduced susceptibility could be attributed to its haploid genome, making it more prone to phenotypic changes upon genetic mutation. *C. lusitaniae*, another haploid *Candid*a yeast, is often associated with resistance to AmB [36,37].

2.1.2 Nystatin—Another polyene used to treat *Candida* spp. infections is nystatin. This compound is not absorbed by the gastrointestinal tract but is also very toxic when provided parenterally and is therefore more commonly used topically [38]. Available in local preparations, its administration has been widely used for treating superficial infections such as oral and vulvovaginal candidiasis [39]. The drug is widely used due to its broad-spectrum antifungal activity [38,40]. Importantly, most *Candida* strains remain susceptible to nystatin. In a study by Fan *et al*., researchers found both *C. albicans* and non-*albicans Candida* isolates from vulvovaginal candidiasis were susceptible to nystatin [41]. A study evaluating oropharyngeal candidiasis by Yu *et al*., 100% of isolates showed susceptibility to nystatin with MIC values of ≤0.015–4 μg/mL against *C. albicans*, 1–4 against *C. glabrata*, 0.125–2 against *C. tropicalis,* and 1–2 against *C. parapsilosis* [42].

Nystatin can present challenges due to drug interactions [43,44]. A recent *in vitro* study performed by Scheibler *et al*. proved that nystatin efficacy to treat oral candidiasis is reduced by chlorhexidine, an antiseptic agent widely used to control oral infections in healthy and immunosuppressed individuals [43]. The combination treatment of nystatin and chlorhexidine affected the efficacy of both drugs at inhibiting *C. albicans* planktonic and biofilms states. The MICs of nystatin and chlorhexidine were higher when these drugs were used sequentially compared to their respective individual MICs. The nystatin-chlorhexidine combination led to hindered reductions in biofilm total biomass compared to individual treatments. HPLC analysis indicated that the concentrations of nystatin and chlorhexidine in mixture were significantly lower than their respective values in single formulations. This was likely a result of increased compound degradation within the mixture formulations.

In spite of drug interaction challenges, nystatin can inhibit fungi as an immunomodulator. Cell membrane lipids play crucial roles in modulating both innate and adaptative immune responses through pathogen recognition, lymphocyte activation, and cytokine signaling [45,46]. Using a vulvovaginal candidiasis model in rats, Zhang *et al*. demonstrated that nystatin treatment enhanced vaginal mucosa immune responses against *C. albicans* by up-regulating IFN-γ-related cellular response, the IL-17 signaling pathway, and IgG-mediated immunity [45]. Therefore, the immunoregulatory role of nystatin presents a promising field that needs further exploration to fully recognize its potential.

2.2 Antifungal azoles

Members of the azole class inhibit 14α-lanosterol demethylase, one of the enzymes responsible for ergosterol biosynthesis, leading to fluidity reduction, alterations in the activity of membrane-associated enzymes, and inhibition of growth that result in cell lysis and death [47]. The azoles consist of two subclasses based on the number of nitrogen atoms in the ring: imidazoles, which contain two nitrogen atoms, and triazoles, formed by three nitrogen atoms [48]. Imidazole was the first to be introduced, but the class now includes miconazole, ketoconazole, tioconazole, butoconazole, clotrimazole, econazole, sertaconazole, and terconazole. These compounds present broad-spectrum activity against different *Candida* spp. with various formulations available [49]; however, due to toxicity, currently, they are recommended for treating superficial candidiasis such as oral and vulvovaginal candidiasis [47,50]. Improvements in the safety profiles were achieved with the creation of the second subclass, triazole. This group includes: fluconazole, itraconazole, voriconazole, and posaconazole [47,51–55].

2.2.1 Fluconazole—Fluconazole and itraconazole are first generation compounds within the triazole subclass. Fluconazole can be provided via oral or parenteral administration, making it amenable for treating a variety of candidiasis infections, such as oropharyngeal, esophageal, peritoneal, vaginal, and disseminated [47]. Fluconazole has high gastrointestinal absorption with similar concentration obtained by endogenous administration. Since fluconazole can reach cerebrospinal fluid and its concentration in urine is higher than serum, fluconazole is used to treat central nervous system and symptomatic cystitis *Candida* spp. infections [56,57]. The use of fluconazole during pregnancy, mainly, in the first trimester should be avoided due to the risk of spontaneous abortion and malformations [58,59]. Taking this into account, the FDA does not recommend using fluconazole at any stage of pregnancy. Another limitation of fluconazole is the pharmacological interaction with certain drugs that can result in decreased efficacy and increased toxicity for one or both administered drugs [60]. Fluconazole-drug interactions have already been described with several drug classes, including tacrolimus, cyclosporine, cisapride, and warfarin [61,62].

The efficacy of fluconazole as well as its convenience and patient tolerance makes this antifungal the first option for the treatment of oral [63] and vulvovaginal candidiasis [63,64]. In a recent meta-analysis study, involving 4,042 participants with oral candidiasis, Fang *et al.* concluded that fluconazole had better mycological cure rate compared to other antifungal drugs: itraconazole, miconazole, clorimazole, ketoconazole, nystatin, and amphotericin B. However, the incidence of recurrence rate and adverse effects were not evaluated by these authors [63]. Qin *et al.* [65] performed a meta-analysis review to compare the effectiveness of different treatments for vulvovaginal candidiasis, including 41 randomized controlled clinical trials. Nine antifungal drugs showed more effectiveness than placebo in the treatment of patients. Fluconazole was the best antifungal drug, followed by clotrimazole, miconazole, itraconazole, ketoconazol, econazole, butoconazole, terbinafine and terconazole. Denison *et al.* showed that the efficacy of oral or topical azole treatments was similar in relation to clinical cure of uncomplicated vulvovaginal candidiasis, however the oral treatment cleared yeast from the vagina better than topical ones [66].

Fluconazole has been shown to be effective in the treatment of 70–80% of *Candida* strains and therapeutic failure is usually associated with susceptibility profile of each *Candida* strain [64]. *C. albicans* and mainly non-*albicans Candida* species are becoming increasingly resistant to fluconazole [64,66]. Therefore, an accurate diagnosis should be performed to guide the selection of the appropriate treatment, including culture confirmation, species identification techniques, and *in vitro* tests of susceptibility to antifungal drugs [64,67]. Nystatin can be used as a treatment option in the case of oral and vulvovaginal candidiasis resistant to fluconazole [67,68]. Other alternatives include flucytosine and AmB creams for vulvovaginal candidiasis and itraconazole, or posaconazole and AmB deoxycholate suspensions for oral candidiasis [57].

In summary, fluconazole has been available for almost three decades; this compound is generic, inexpensive and largely safe outside of pregnancy. Limitations are few in terms of toxicity, but shortcomings for treating mucosal infections can occur due to resistance in non-*albicans Candida* species and more recently *C. albicans.*

2.2.2 Itraconazole—Like fluconazole, itraconazole is also available for oral and intravenous use; however, it has poor aqueous solubility and low bioavailability [69]. Thus, it is recommended for fluconazole refractory *Candida* infections [57]. In 2018, a new oral formulation, SUBA itraconazole capsules (SUper BioAvailability), was approved by the Food and Drug Administration (FDA). This new formulation is based on a polymeric matrix that controls itraconazole release in the duodenum, improving dissolution and absorption [70,71]. In prophylaxis for stem cell transplantation and treatment for hematological malignancies patients, the SUBA®- itraconazole formulation presented more rapid therapeutic levels and less inter-patient variability in comparison to the traditional itraconazole formulation [71].

2.2.3 Voriconazole and Posaconazole—Voriconazole and posaconazole are members of the second generation triazoles, mainly developed to address emergent fluconazole and itraconazole resistance. These compounds are considered fungicidal, have a broader spectrum of activity compared to the earlier azoles, and are indicated for oropharyngeal and invasive candidiasis [57,72]. They have demonstrated *in vitro* activity against most *Candida* species [73]. Rodrigues *et al.* verified that voriconazole was notably more effective than fluconazole against *C. glabrata* biofilms, in which voriconazole had better diffusion through the biofilms and higher cell penetration capacity [54]. Although voriconazole and posaconazole demonstrates fungicidal activity and broader spectrum than fluconazole in *in vitro* studies, there is little comparative clinical data among these antifungals. El-Ghmmaz *et al.* [74] compared the effectiveness of voriconazole and fluconazole in preventing invasive fungal infections in 70 patients undergoing hematopoietic stem cell transplantation. The prophylaxis with voriconazole did not differ from fluconazole regarding the prevention of invasive fungal infections and overall survival. Devanlay *et al.* [75] analyzed the posaconazole and fluconazole as primary prophylactic antifungal agents in 91 patients with acute myeloid leukemia. The results did also not distinguish any difference between posaconazole and fluconazole prophylaxis. However, mycological examination of

stools showed an increased colonization by non-*albicans Candida* species in patients treated with fluconazole, suggesting a selection pressure on *Candida* growth by this antifungal.

Voriconazole and posaconazole are available in oral and intravenous formulation [57,72]; however, their pharmacokinetics represent a therapeutic challenge [52,76]. Voriconazole has good oral bioavailability, but its absorption can be influenced by food [57]. Posaconazole provides a delayed-release tablet formulation with improvements in absorption [77], reaching more serum drug concentration and higher efficacy than oral suspension formulation [77,78]. Both antifungals exhibit highly variable inter- and intra-patient pharmacokinetics, and numerous factors have been associated with their variability in plasma levels, such as altered intestinal absorption, drug interactions, diarrhea, chemotherapy, age, and weight [76].

In a recent study, Hachem *et al.* compared the safety and efficacy of voriconazole and posaconazole as prophylactic drugs for invasive fungal infection in 200 patients with hematological malignancies in the U.S. [79]. The efficacy was very similar between the groups with comparable mortality rates. However, symptomatic adverse effects were more frequent in the voriconazole group, while posaconazole was better tolerated by patients. Unfortunately, liver function abnormalities were more common in the posaconazole group. Other specific adverse effects have been reported for these antifungals. The administration of voriconazole was associated with skin photosensitivity [80] and increased risk for cutaneous squamous cell carcinoma in patients who underwent lung and hematopoietic cell transplants [81–83]. Parkers *et al.* reported visual hallucinations and neurological disturbances in a patient with high posaconazole concentration in serum, suggesting that patients treated with new formulations of posacanozole should be monitored for visual and central nervous system (CNS) alterations [84].

2.2.4 Isavuconazole, Ravuconazole, and Albaconazole—More recently, additional triazole agents were developed, including isavuconazole, ravuconazole, and albaconazole [47,85]. Isavuconazole is available in oral or intravenous administrations and use for invasive candidiasis was investigated in a recent Phase 3 clinical trial (Clinicaltrials.gov, NCT00413218), in which the treatment with isavuconazole showed similar efficacy and safety to the treatment with caspofungin followed by voriconazole [86]. In another clinical trial (Phase 2), isavuconazole also exhibited comparable efficacy and safety to fluconazole for the treatment of esophageal candidiasis [87]. Ravuconazole and albaconazole are undergoing clinical trials for use in intravenous and oral formulations, respectively [88]. Both antifungals present promising effects for the treatment of fungal infections caused by fluconazole and itraconazole resistant strains [88].

2.2.5 Azole resistance—Due to the numerous advantages of the azoles, this antifungal class has been used as a gold standard therapy for over 50 years; however, this has resulted in the global emergence of resistant strains [89–92]. Azole resistance mechanisms developed by *Candida* spp. have widely been investigated, and currently three main mechanisms are described: (1) overexpression of membrane transporters [85,93,94]; (2) alterations of ergosterol biosynthesis [95,96]; and more recently, (3) alterations in sterol import [97].

Overexpression of membrane transporters is an important resistance mechanism of *Candida* spp. to azole agents. Two classes of membrane transporters in *Candida* cell membrane have been associated to azole resistance: ATP binding cassette (ABC) and major facilitator superfamily (MFS). Both classes are integral cell membrane proteins with different mechanisms of obtaining energy to drive efflux of substrates as azoles. The ABC proteins are primary active transporters that employ energy from the hydrolysis of ATP, while MFS proteins are secondary active transporters that use a proton gradient from the cell membrane as an energy source to efflux drugs [94,98]. The increased expression of ABC and MFS transport proteins have been correlated, respectively, with the overexpression of *Candida* spp. drug resistance genes (*CDR1* and *CDR2*) and multi-drug resistant genes (*MDR1* and *MDR2*) [98]. The overexpression of *CDR* and *MDR* genes was correlated with decreased azole susceptibility in several *Candida* spp., such as *C. albicans* [99], *C. glabrata* [100], *C. parapsilosis* [101], and *C. auris* [102].

Azoles also exert less efficacy when there are alterations to ergosterol biosynthesis, leading to decreased affinity to the fungal cell target [95]. Erg11 is an essential enzyme that regulates the ergosterol biosynthesis pathway. Mutations in *ERG11* cause amino acid substitutions that result in proteins being unable to binds to azoles, consequently generating azole resistance [94]. Flower *et al*. sequenced *ERG11* for 63 *C. albicans* fluconazole resistant isolates and observed that 87% presented at least one mutation in the *ERG11* gene [96]. A number of amino acids substitutions have been correlated to azole resistance: A114S, Y132H, Y132F, K143R, Y257H, K143Q, F145L, S405F, D446E, G448E, F449V, G450E, and G464S [95,96]. In a recent multicenter study, Chowdhary *et al*. found 90% of fluconazole resistant *C. auris* isolates among 350 strains were caused by amino acid substitutions Y132 and K143 in *ERG11* [103].

Fungal cells exposed to azoles must synthesize more endogenous ergosterol or import exogenous sterol to survive antifungal treatment [94,97]. In 2018, Lin *et al*. showed that the presence of exogenous cholesterol or ergosterol in growth media made *C. glabrata* strain highly resistant to fluconazole and voriconazole. In contrast, *C. glabrata* mutant strain lacking the *AUS1* gene that encodes a sterol influx transporter exhibited hypersensitivity to azoles [97]. Therefore, *Candida* spp. can scavenge free sterols for the cell membrane as cholesterol, acquiring resistance to azole antifungals.

2.3 Echinocandins

Echinocandins inhibit (1,3) β-D glucan synthase (encoded by *FKS* genes) that are responsible for the biosynthesis of glucan, the major polysaccharide present in the fungal cell wall. The absence of this target polysaccharide in human cells results in low toxicity. Other advantages of this antifungal class includes low propensity for drug-drug interactions and rapid fungicidal activity against *Candida* spp., including triazoles-resistant clinical isolates. The available echinocandins are caspofungin, micafungin, and anidulafungin. All the echinocandins have large molecular weight and are available in intravenously formulations; thus, the absence of an oral formulation is a limitation of this antifungal class [104–107].

Candida spp. resistant to echinocandins are uncommon; varying from 1 to 10% of the total isolates depending on the species analyzed [108–110]. Recent data indicate that the resistance rates to echinocandins have remained low for most *Candida* isolates: *C. albicans* (0–0.1%), *C. tropicalis* (0.5–0.7%), and *C. krusei* (0–1.7%) [89]. *C. lusitaniae*, *C. parapsilosis*, and *C. guilliermondii* are known to have reduced susceptibility to echinocandins, and *C. glabrata* is considered the most resistant species associated with treatment failures [111–113]. *C. glabrata* has shown an increase in resistance in recent years, reaching rates of 8 to 11% [89]. Resistant *C. glabrata* isolates tended to be non-susceptible/resistant to at least two echinocandins [89] and can exhibit cross-resistance to fluconazole [113]. *Candida auris*, also well known for fluconazole resistance, exhibits variable susceptibility to echinocandins with resistant rates reported at 2–7% in India, 4% in the U.S., and 7% among isolates collections from Pakistan, South Africa, and Venezuela [103,114,115].

Candida spp. resistance to echinocandins occurs due to mutations in *FKS* genes (*FKS1* and *FKS2*), which are responsible for the expression of the (1,3) β-D glucan synthase. Hot spot mutation regions in *FKS1* have been observed for *C. albicans*, *C. krusei*, *C. parapsilosis*, and *C. auris* [103,110,116–120], while mutations on both *FKS1* and *FKS2* were reported for *C. glabrata* [118]. Acquired resistance to echinocandins has also been associated with a compensatory increase in cell wall chitin in response to inhibition of (1,3) β-D glucan by this antifungal class [112,113]. Walker *et al.* demonstrated that the *in vitro* treatment of *C. albicans* with a sub-MIC level of caspofungin led to an increase in chitin content, that resulted in a reduction of susceptibility to caspofungin [112]. Using a mouse model of systemic candidiasis, Lee *et al.* verified that after 48 h post-infection, caspofungin treatment induced an increase in chitin in *C. albicans* cells recovered from kidneys [121]. In addition, some of the recovered clones had acquired a point mutation in *FKS1*. The authors suggested that two non-exclusive mechanisms can affect echinocandins sensitivity: acquisition of *FKS1* mutations and elevation of chitin levels via the stimulation of cell wall integrity pathways. In 2020, Walker *et al.* showed that increased chitin exposure in *C. albicans* cells, in response to caspofungin treatment, altered cytokine production by macrophages, suggesting that cell wall remodeling influences host immune responses [113]. Therefore, the understanding about the gene mutations and wall remodeling processes during *Candida* spp. infection can provide new perspectives to improve the drug efficacy [121].

Efficacy among *Candida* isolates and low toxicity profiles means echinocandins are recommended as the first line defense for treatment of suspected or documented candidemia and invasive candidiasis [57,122]. This recommendation is supported by clinical trials that reported echinocandins class superiority compared to other antifungal classes when treating invasive *Candida* infections [123,124]. Additionally, recent studies demonstrated that echinocandins are capable of eradicating *Candida* biofilms, providing an interesting therapy option for catheter-related *Candida* biofilm infections [125–127]. Basas *et al.* compared the efficacy of anidulafungin with amphotericin B (L-AmB) in the treatment of *C. albicans* and *C. glabrata* biofilms, using *in vitro* and *in vivo* models [126]. Anidulafungin exhibited greater inhibitory activity than L-AmB against biofilms formed *in vitro* on silicone discs. The minimum biofilm eradication concentration for 90% ($MBEC_{90}$) of anidulafungin was > 100-fold and > 1000-fold more effective than L-AmB for *C. glabrata* and *C. albicans* strains,

respectively. In the *in vivo* study, central venous catheters were inserted into rabbits infected by *Candida* strains. Antifungal lock therapy with L-AmB and anidulafungin were able to reduce fungal burden at a similar capacity against *C. albicans*; however, anidulafungin was more effective than L-AmB against *C. glabrata.*

3 Therapeutic approaches in development

3.1 New antifungal compounds

To overcome the limitations with currently available treatments new synthetic and natural antifungal compounds have been investigated [128]. For all types of compounds, the main challenges involve the identification of substances with broader antimicrobial spectra and action mechanisms that limit the emergence of resistant strains, while maintaining good pharmacokinetic and low toxicity [129–131].

3.1.1 Structure modifications to existing antifungal classes

3.1.1.1 Modified amphotericin B: Many of the new synthetic compounds focus on structural modifications in the already available drugs, including polyenes, azoles, and echinocandins. Among them, enchochleated amphotericin B (Coch-AmB) is a new formulation that includes this polyene in cochleates (phospholipid spiral multilayered structure), providing oral administration of amphotericin B. The efficacy of Coch-AmB was demonstrated in systemic candidiasis mouse model [132], and the compound is currently undergoing safety and efficacy evaluation in patients with vulvovaginal candidiasis in a phase 2 clinical trial [129].

3.1.1.2 Modified Azoles: A large number of antifungal compounds have been developed based on modified azoles structures [133,134]. Shrestha *et al.* modified fluconazole by replacing one of the triazole rings with a linear alkyl chain and by adding different structures on the phenyl ring, generating compounds active against *Candida* spp. and less cytotoxic to mammalian cells according to *in vitro* assays [133]. Xie *et al.* synthesized twenty-nine novel triazole analogues of ravuconazole and isavuconazole, verifying that most of them showed *in vitro* antifungal activity, including activity against *C. albicans*, *C. glabrata*, and *C. parapsilosis* strains [134]. Based on the structure-activity relationships (SAR) analyses, these authors concluded that the most effective compounds were achieved by replacing the 4-cyanophenylthioazole moiety of ravuconazole with fluorophenylisoxazole [134]. Other researchers designed tetrazoles with metal-binding groups, resulting in molecules more selective for fungal sterol biosynthesis and with longer half-lives, designated as tetrazoles VT-1598, VT-1129, and VT-1161 [135,136]. All of them showed promising results in preclinical studies, and VT-1161 (Oteseconazole) is currently in a phase 3 clinical trial for the treatment of vulvovaginal candidiasis [137]. Tetrazoles have showed potent *in vitro* and *in vivo* inhibitory activity against azole-and echinocandin-resistant *Candida* isolates, including *C. glabrata*, *C. krusei* and *C. auris* [137–139]. Furthermore, VT-1161 demonstrated excellent efficacy and safety in a murine model of vulvovaginal candidiasis, with high volume of distribution, high oral absorption, long half-life, and rapid penetration into vaginal tissues [140].

3.1.1.3 Modified Echinocandins: Structural modifications of echinocandins have also been generated. Rezafungin, is a new antifungal derived from anidulafungin that is in phase 2 clinical trial to test efficacy against candidemia and invasive candidiasis. The stability that provides a longer half-life along with a favorable safety profile permits rezafungin to be administered weekly rather than daily. This extended release drug should reduce patient hospitalization times by altering therapeutic regimens. In addition, rezafungin has efficacy for treating less-susceptible fungal pathogens and shows low propensity to induce antifungal resistance [141]. Hager *et al.* demonstrated that rezafungin was more potent than amphotericin B and micafungin against *C. auris,* reducing kidneys fungal burden in immunosuppressed mice. In this report, rezafungin (20 mg/kg) was administered on alternating days, while amphotericin B (0.3 mg/kg) and micafungin (5 mg/kg) were given daily. The data suggest that rezafungin can inhibit *C. auris* even when provided in less frequent doses [142].

3.1.2 Development of new antifungal classes—In addition to developing antifungals derived from polyenes, azoles, and echinocandins, new antifungal classes have been introduced in the last years (Figure 1) [137]. Among them, enfumafungin is an antifungal targeting the cell wall by inhibiting the (1,3)β-D glucan synthase. Although, enfumafungin shares the same drug target with echinocandins, this compound presents a structurally distinct antifungal class [143]. Enfumafungin is a glycosylated fernene-type triterpenoid produced by the fungus *Hormonema carpetanum*. Due to the potent antifungal activity, enfumafungin is being employed in the development of the antifungal ibrexafungerp (SCY-078) [144]. The advantages of SCY-078 are the possibilities of both intravenous and oral administrations and the fungicidal activity against *Candida* spp., including strains resistant to azoles and echinocandins [129,145–150]. SCY-078 oral formulation is in clinical trial to treat invasive and vulvovaginal candidiasis [144]. Azie *et al*. reported that ibrexafungerp has numerous attributes for the treatment of vaginal candidiasis, including oral one-day dose, high tissue penetration, increased activity at low pH, low risk for drug-drug interactions and reduced toxicity [151].

Another promising antifungal is manogepix (fosmanogepix APX001A), which inhibits Gwt1, an enzyme required in the glycosylphosphatidylinositol biosynthesis pathway, a component present in the yeast cell wall and membrane [52,152]. This compound has exhibited broad-spectrum activity against *Candida* spp., except for *C. krusei* [153,154]. Efficacy against *C. auris* has also been demonstrated in *in vitro* and *in vivo* studies and phase 2 clinical trials are ongoing [154–156]. A concern has been brought to light through a new study which identified two efflux-mediated mechanisms in *C. albicans* and *C. parapsilosis* that were associated to decreased manogepix susceptibility [157], suggesting the potential for resistance or reduced efficacy that will need to be monitored.

Since the cell wall and plasma membrane are the main targets of antifungal drugs, some researchers have focused on the development of antifungals with alternative target sites, such as arylamidine T-2307 [48,52,158]. Arylamidine mode of action inhibits the respiratory chain, compromising cell energy production [159]. In a study by Mitsuyama *et al.*, arylamidine T-2307 exhibited potent inhibition against *C. albicans*, including fluconazole resistant strains, and showed efficacy in the treatment of disseminate candidiasis in a mouse

model [160]. More recently, Wiederhold *et al.* demonstrated arylamidine T-2307 inhibitory activity against *C. auris* in a mouse model, in which treatment improved the survival rate and reduced the kidney fungal burden compared to an untreated group [158].

3.1.3 Identification of new bioactive molecules from natural products—

Natural compounds have always been important sources of new antimicrobial drugs [161–163]. Since the first modern antimicrobial agents, many antibacterial and antifungal drugs have taken the form of semi-synthetic derivatives of natural products [162], including two relevant antifungal classes: polyenes and echinocandins [128]. Natural product drug discovery is an intensive labor that requires the isolation and characterization of several bioactive molecules [161,162]. The feasibility of high-throughput screening shifted research focus to synthetic compound libraries, but the current emergence of multi-drug resistant strains is reviving attention for natural compounds in academic and biotechnology sectors [162].

Most natural compounds investigated include extracts from plant or microbial origins [161,164–166]. In a systematic review, Singla *et al.* showed that plants from the order Lamiales, Apiales, Asterales, Myrtales, Sapindales, Acorales, Poales and Laurales exhibit antifungal activity against *Candida* spp. [161]. Likewise, antifungal activity has been reported from different microorganisms, such as *Lactobacillus* spp. [166] and *Streptococcus* spp. [165,167]. Antifungal activities has been associated with compounds belonging to the terpenoids, phenylpropanoid, alkaloids, flavonoids, polyphenol, naphthoquinone and saponins classes, but their mechanisms of action and possible synergism with antifungal drugs still need to be investigated for complete elucidation [161].

3.1.4 Search for compounds targeting *Candida* spp. virulence mechanisms.

—Another attractive antifungal approach is the identification of compounds targeting specific *Candida spp.* virulence mechanisms. The advantages to treat candidiasis with anti-virulence agents include the preservation of the host normal microbiome, as well as lower toxicity and reduced selective pressure for developing resistance in relation to drugs that target fungal growth [168–175]. Moreover, anti-virulence strategies can have a substantial impact for both prophylactic and therapeutic management of candidiasis [169]. In this context, many authors have sought inhibitors of hydrolytic enzymes, morphogenesis, adhesion and biofilm formation [171].

To identify new antifungal agents targeting virulence mechanisms, Bonvicini *et al.* investigated some compounds of chalcones that are precursors of flavonoids. Forty chalcone-based analogues were screened against *C. albicans*, and two compounds (5 and 7) were capable of weakening its pathogenicity factors. Both compounds inhibited hyphae and biofilm production, indicating a potential use in anti-infective therapeutics [168]. Romo *et al.* screened 30,000 drug-like small-molecule compounds from the DIVERSet library (ChemBridge Corporation), identifying N-[3-(allyloxy)-phenyl]-4-methoxybenzamide (9029936) as the major compound with inhibitory activity against filamentation and biofilm formation of *C. albicans* [173]. Prasath *et al.* investigated the effects of palmitic acid on the virulence factors of *C. tropicalis.* After 48 h of treatment, palmitic acid decreased the enzymatic activity, leading to a reduction of 53 to 72% of lipase production and a total

inhibition of protease production. The authors suggested that palmitic acid can be applied to increase the efficacy of conventional antifungal drugs in the control of non-*albicans Candida* species [176].

3.2 Drug repurposing

Drug repurposing is an interesting strategy to investigate new uses of existing compounds [177,178]. Two principles support the drug repurposing concept: 1) many active drugs are not fully understood and 2) there are common molecular and genetic factors between different pathologies [179]. Since repurposed candidates have already been evaluated for pharmacokinetic, pharmacodynamic, and toxicological effects, the process is faster and cheaper compared to traditional novel drug discovery [177,179–181]. Within this context, a number of off-patent compound libraries have been screened to find antifungal agents, evaluating effects on fungal growth, morphogenesis, and biofilm formation of *Candida* spp., as well as synergistic action with antifungal drugs. To date, various compounds with inhibitory activity against *Candida* spp. have been identified including antimicrobial (antibacterial and antiviral) agents and non-antimicrobial pharmacological classes [182–186].

3.2.1 Antimicrobial agents—Repositioning antibacterial drugs as antifungal is considered a promising strategy for treating candidiasis [182,183], and in some cases, candidate compounds can also be employed for the dual purpose for treating mixed infections caused by bacteria and fungi [182]. Jadhav *et al.* found that moxifloxacin, an antibacterial fluroquinolone, can decrease both planktonic and biofilm states of *C. albicans*, as well as inhibit the yeast to hyphal transition [182]. Interestingly, the moxifloxacin antifungal mechanism of action was multi-targeted. Moxifloxacin exhibited good binding to the active sites of *C. albicans* topoisomerase II, an enzyme associated with DNA replication, and also affected a number of genes involved in *C. albicans* morphogenesis via MAPK and cAMP-PKA pathways [182].

Among a total of 21 sulfa antibacterial drugs, Eldesouky *et al.* [183] found 15 compounds with anti-*Candida* activity. These compounds exhibited synergistic action with fluconazole against *C. albicans* fluconazole resistant isolates in both *in vitro* assays and a *Caenorhabditis elegans in vivo* model. Synergistic activity was attributed to dihydropteroate synthase (DHPS) enzyme inhibition by sulfa drugs, leading to restriction of the *Candida* ergosterol biosynthesis pathway and, consequently, improving the effect of fluconazole [183].

Boron containing compounds have known antibacterial activity [187] and the boric acid has been clinically used as topical antifungal agent for vulvovaginal candidiasis caused by azole resistant *Candida* strains [64]. Based on this evidence, recently, Rossoni *et al.* tested the antifungal effects of surface pre-reacted glass-ionomer (S-PRG) eluate that is used in dental materials to suppress cariogenic bacteria and reduce dental plaque accumulation. S-PRG is a material that releases six types of ions, BO_3^{3-} (Borate), Na^+, Sr^{2+}, SiO_3^{3-}, Al^{3+} and F^-, in the oral cavity. S-PRG eluate exhibited antifungal activity against *C. albicans*, *C. glabrata*, *C. krusei,* and *C. tropicalis*, reduced *in vitro* biofilm formation and protected *G. mellonella*

against experimental candidiasis, demonstrating therapeutic potential for oral candidiasis [188].

Antiviral drugs have also been studied for repurposing potential. Yousfi *et al.* focused their studies on ribavirin, a guanosine analog with broad-spectrum activity against RNA and DNA viruses that is commonly used for the treatment of hepatitis C virus (HCV) [189]. Ribavirin exhibited antifungal activity against 63 *Candida* spp. isolates among 100 isolates tested. *C. parapsilosis and C. tropicalis* demonstrated the greatest susceptibility. Promisingly, ribavirin was effective against multidrug-resistant *C. albicans* and showed synergistic action with fluconazole, itraconazole, and posaconazole [189].

Other investigational agents for antifungal use include HIV-protease inhibitors, such as indinavir, ritonavir, and saquinavir [184,190,191]. Studies that investigated these compounds note clinical evidences that treatment of HIV positive patients with protease inhibitors results in improved mucosal *Candida* infections, with direct effect on fungi rather than augmenting host immune status [192]. Cassone *et al.* demonstrated that indinavir and ritonavir were able to reduce the growth and secretory aspartic proteases (Sap) production by *C. albicans*, as well as inhibit the development of vaginal candidiasis in rats with an efficacy comparable to fluconazole [190]. Calug *et al.* reported a significant structural similarity between *C. albicans* Sap2 and HIV-1 protease, inciting the development of a single inhibitory drug able to interact with both viral and fungal targets [191].

3.2.2 Non-antimicrobial agents—Several studies have reported antifungal properties from pharmacological classes that lacked antimicrobial characterization, including anti-inflammatory, anticancer, antidepressant, antipsychotic, anesthetics, antihyperlipidemic and others (Table 2). As an example, auranofin, an anti-inflammatory drug used to treat rheumatoid arthritis [193], was investigated by Fuchs *et al.* as a repurposed antibacterial and antifungal agent [185]. Auranofin was capable of inhibiting Gram-positive bacteria, as well as fungal species, such as *Candida* spp. Auranofin inhibited thioredoxin reductase, part of the thioredoxin system responsible for protecting microbial cell against oxidative stress. Since the thioredoxin system is conserved in both prokaryotic and eukaryotic organisms, auranofin can be the initiate of a future class of antibiotics and antifungals based on this new microbial target [185,194,195].

Seeking additional repurposing antifungals, Sun *et al.* investigated NSC319726, a thiosemicarbazone anticancer agent [196]. This compound had antifungal activity against *Candida* spp. in the range of 0.1 – 2.0 μg/mL and synergistic action with fluconazole, itraconazole, and voriconazole. Using a high concentration of NSC319726, synergistic activity was also found with caspofungin. Through transcriptome analysis, NSC319726 mechanism of action was correlated to ribosome biogenesis inhibition and induction of oxidative stress [196]. In another study, Gouri *et al.* investigated the antifungal action of sertraline, a compound used to treat of depression, against three *C. auris* strains resistant to fluconazole and amphotericin [197]. In additional to significantly inhibiting planktonic cultures, sertraline impaired fungal morphogenesis and biofilm formation. The mechanism of action against *C. auris* was explained by the binding nature of sertraline to the sterol 14

alpha demethylase, which is involved in ergosterol biosynthesis. Therefore, this compound presents a new, promising antifungal against emergent drug resistant *C. auris* [197].

3.3 Combination therapy

In contrast to the usual candidiasis treatment with a single antifungal agent, new approaches employing multiple therapeutic agents (a “drug cocktail”) present an opportunity to overcome fungal resistance by engaging multiple targets [198,199]. Developing resistance to multiple deployed agents becomes more difficult because the fungal cells are less capable of compensating for the actions of two or more drugs or acquire mutations in multiple genes without adverse impact to cell survival or fitness [199,200]. Combined therapies seek synergistic effects that enhance the antifungal activity directly and/or adjunct effects that alter the susceptibility of *Candida* cells to the antifungal drug, reverting resistance status [179,201]. These treatments can employ a combination of two antifungal drugs or a combination of antifungal drug with new compounds [198,200,202].

3.3.1 Available antifungal drug combinations—The combination of antifungal drugs are an interesting approach since the synergistic effects can reduce therapeutic dosages, and therefore, decrease toxicity and side effects caused by high doses of a single drug [198]. Reginatto *et al.* tested the effects of combining anidulafungin and amphotericin B treatments against *Candida* biofilms formed *in vitro* on venous catheter [203]. The combination of these antifungals at lower concentrations had a significant increase in the antifungal activity in relation to the individual agents. The use of anidulafungin (0.5 μg/mL) or amphotericin B (2.5 μg/mL) individually were able to inhibit 37–75% and 49–68% of the biofilms, respectively, while the combination of anidulafungin and amphotericin B, at the same concentrations, reached 94–100% of biofilm inhibition. To obtain similar reductions with anidulafungin alone, it was necessary to use this antifungal at higher concentration (1 μg/mL), indicating that the combined therapy can decrease the toxicity caused by the isolated treatments.

Despite the *in vitro* evidences, until now, few clinical studies evaluated the efficacy of combined systemic antifungal drugs for candidiasis treatment. Recently, Ahuja *et al.* reported two cases of endovascular infections caused by *C. parapsilosis* in patients with prosthetic valves who responded positively to combination antifungal therapy without surgical intervention [204]. One patient was treated with micafungin and fluconazole, while the other one was treated with micafungin, fluconazole, and flucytosine. The use of combination therapies in both patients resulted in successful treatment without the need for surgical intervention, suggesting that they could pose a useful approach for the patients with endovascular infections.

Amphotericin B and 5-fluorocytosine (5-FC) have been used in combination to treat invasive candidiasis. Since the concurrent delivery of these antifungals by intravenous administration is precluded due to drug precipitation, recently Alvarez *et al.* developed a formulation that facilitates co-delivery of AmB and 5-FC using PEG-lipid poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE) micelles. The formulation developed showed efficacy in reducing the fungal burden of neutropenic mice with disseminated

candidiasis [205]. The commercial availability of formulations with combined components can incite future clinical trials.

3.3.2 Combination of antifungal drugs with new compounds and therapies—

Studies have also been conducted to identify compounds that can act synergistically with antifungal drugs. Using the natural antimicrobial agent lactoferrin from human mucosal secretions, Fernandes *et al.* found a synergistic effect with AmB against a diverse range of yeasts, including *C. parapsilosis c*omplex, *C. dubliniensis, C. tropicalis*, and *C. albicans* [206]. The associated therapy reduced MIC values 8-fold for lactoferrin and 4-fold for AmB. Moreover, the combination of these compounds was effective in *G. mellonella* infected by *C. albicans*, prolonging survival in 93% of larvae past 10 days and reducing fungal burden 5-fold compared to amB alone [206].

The known antifungal fluconazole was combined with ginkgolide B extracted from the *Ginkgo biloba* leaf by Li *et al.* who verified a synergistic effect against *C. albicans* in planktonic and biofilm states, and also found the dual application efficacious in the *G. mellonella* infection model [198]. Ginkgolide B also increased the antifungal effect of fluconazole on azole-resistant *C. albicans*, reducing the MIC of fluconazole from > 512 μg/mL to 0.25–1 μg/mL, with the fractional inhibitory concentration index (FICI) ranged from 0.06 to 0.25. The synergistic effect resulted in phenotypic effects characterized by reduced filamentation, disruption of intracellular calcium, and inhibition of drug efflux pumps [198].

In addition to traditions chemical interactions, photodynamic chemicals have also exhibited beneficial effects when applied in combination with antifungal agents. Photochemicals are applied as inert compounds that are induced to an excited electron state when light is applied. Interestingly, Chibebe Junior *et al.* married fluconazole treatment to photodynamic therapy (PDT) using methylene blue to produce reactive oxygen species when excited [207]. For this process, *G. mellonella* larvae were infected by a fluconazole resistant *C. albicans* strain, and subsequently, treated with fluconazole in combination with methylene blue activated by red light irradiation. Larvae treated with a combination of PDT and fluconazole showed 50% survival at the end of the experiment (7 days) compared to control groups treated with fluconazole or PDT alone that resulted in 100% mortality. The prolonged survival reached by the combination therapy suggested that permeabilization on the fungal cells caused by PDT make *C. albicans* more susceptible to fluconazole. The combination of antifungal drug with PDT can be a promising approach in the treatment of mucosal candidiasis.

3.4 Nano-particulate drug delivery systems

Currently, the products obtained from nanotechnology provide interesting physiochemical characteristics enabling its applications in different health-care areas [208,209]. Nanoparticles are nanometer size particles that serve to transport drugs that are dissolved, entrapped, encapsulated, adsorbed, or chemically attached to carriers [210,211]. The use of nanoparticles can improve bioavailability of antifungal drugs because their small size facilitates reaching the vascular system and tissues [209,212]. Additionally, it has been reported that nanoparticles can contribute in overcoming microbial drug-resistance since

antifungal compounds loaded in specific formulations avoid drug recognition by efflux pump proteins, keeping the drug inside fungal cells where it can be most effective [213].

Solid lipid nanoparticles (SLN) are a drug delivery system composed of biodegradable lipids prepared from oil-in-water nanoemulsions, which enable higher drug penetration, better contact with the cell target, and controlled liberation of the antifungal [213,214]. Moazeni *et al*. demonstrated that solid lipid nanoparticles loaded with fluconazole were capable of reducing the MIC values for fluconazole-resistant strains by 4, 8 and 4 folds, respectively for *C. albicans*, *C. parapsilosis*, and *C. glabrata* [213].

Nanostructured lipid carriers (NLC) present another transport option and are synthetized using solid lipids incorporated into liquid lipids, resulting in nanostructures with improved drug incorporation and time release properties. The liquid oil droplets in a solid matrix increase the loading potential in comparison to SLNs [209]. Jansook *et al*. compared amB-loaded in SLN and NLC with the commercially available amB colloidal dispersion (Fungizone®) [215]. Both nanoparticles formulations had similar *in vitro* antifungal activity reducing the MIC value by 4 folds compared to Fungizone®. Moreover, the lower hemolytic activity and lower aggregate formation capacity demonstrated that these nanoparticles could be less toxic than Fungizone® [215].

In addition to lipidic nanoparticles, polymeric systems have also been developed for drug delivery [216]. Polymeric nanoparticles are obtained from natural polymers (eg, chitosan, gelatin, and alginate) or synthetic polymers (polylactide, poly lactide-co-glycolide, copolymers, and polyacrylates), and are able to protect drugs from degradation or prevent side effects from toxicity [209,217]. El Rabey *et al*. used fungal chitosan extracted from *Amylomyces rouxii* to synthetize nanoparticles, which were later loaded with fluconazole [218]. Fluconazole was slowly released from the synthesis of chitosan nanoparticles in the first hours (3.4% after 3 h and 11.3% after 5 h) followed by a substantial increased after 12 h (94.8%), exhibiting significant antifungal activity against strains of *C. albicans*, *C. parapsilosis,* and *C. glabrata* resistant to fluconazole, itraconazole, and voriconazole [218].

Another promising nano-particulate drug delivery system involves metals that have intrinsic antimicrobial properties such as gold (Au), silver (Ag), and zinc (Zn) [219–222]. Metal-based nanoparticles show unique physicochemical properties that provide magnetic field-controlled drug delivery carriers [222]. Hussain *et al*. proved the enhanced antifungal efficacy of nystatin or fluconazole after conjugation with silver nanoparticles (NS) [221]. This conjugation increased the inhibition percentage of *C. albicans* in a dose-dependent manner reaching 90–100% for both nystatin-SN and fluconazole-SN formulations at 200 μg/mL. In addition, no cytotoxicity for human cell lines was observed, suggesting that metal nanoparticle formulations could be a safe and effective alternative to improve the efficacy of the current antifungal treatments [221,223].

4 Conclusion

Despite great advances in the medical field, morbidity and mortality rates associated with *Candida* spp. are still high. Treatments for these infections remain limited to only three

major antifungal classes, polyenes, azoles, and echinocandins, which address a large variety of clinical manifestations (superficial, mucosal, systemic and invasive candidiasis), and thus must be deployed in different ways. These antifungal classes have been widely used over many years seeking to reach a counterbalance between their effectiveness and limitations related to pharmacokinetics and cytotoxicity. However, the exhaustive use of these limited antifungals leads to development of drug resistance mechanisms by fungal cells. Motivated by the rapid emergence of resistant strains, several researchers have introduced new antifungal agents and raised attractive therapeutic options for candidiasis, exploring structural modifications on polyenes, azoles and echinocandins, synthesis of different antifungal classes, drug repurposing, combination therapies, and drug delivery systems.

5 Expert opinion

The emergence of antifungal drug resistance is the biggest challenge when trying to treat candidiasis. The prevalence of antifungal resistance varies according to *Candida* species with greater prominence found among non-*albicans Candida* species. Recently, the most significant concerns about antifungal resistance has been the emergence of multi-drug resistant *C. auris* strains. *C. auris* was first described in Japan (2009) and rapidly spread across the 5 continents [224,225]. Most reports of *C. auris* infections involve critically ill hospitals patients that result in high mortality rates due to limited treatment options [224,226]. *C. auris* presents high level of antifungal resistance with reduced susceptibility to azoles, polyenes and even echinocandins. For example, Ostrowsky *et al.* found 99.7% of *C. auris* isolates resistant to fluconazole, 63.4% resistant to AmB, and 3.9% resistant to echinocandins from hospitalized patients in USA [114]. During the treatment of these patients with antifungal medications, some *C. auris* strains became resistant to the three antifungal classes. Troublingly, the progressive isolation of strains resistant to the all three antifungal classes shifts *C. auris* from multidrug resistance to pan-resistance status. The emergence of pan-resistant *C. auris* strain is an alarming signal for the necessity of new therapeutic options.

To improve the therapeutic approaches for candidiasis, many researchers have explored alternative means to deploy the available arsenal. Among them, recent studies have investigated different drug delivery systems for polyenes, azoles or echinocandins that provide localized targeted delivery that consequentially results in reductions antifungal dosages. The development of new liposomal, colloidal, and polymeric carriers represents a promising approach to increase the effectiveness and to counteract emerging resistance for all antifungal classes. In addition, new ways of approaching targets are coming into focus, such as the capacity of polyenes to extract sterols from the fungal cell membrane (sterol sponge model) and the ability of echinocandins to increase fungal cell wall chitin exposure. Approaches that remodel fungal cell surfaces suggest that these antifungals can have an important role provoking immune responses so cells are not so stealth in the body. Thus, bolstering antimicrobial chemotherapy with enhanced or altered immune responses.

The most significant impact anticipated in the field is always the introduction of new antifungal compounds, a situation that has been in an extended drought. There are however, a few antifungal compounds in clinical trials, yet the number pales in comparison to other

disease indices. Most of candidate drugs include synthetic compounds with mechanisms of action focused on targeting the plasma membrane or cell wall. These compounds include structural modifications of the available antifungal classes (Coch-AmB, tetrazoles VT-1598, VT-1129, VT-1161 and rezafungin) or new antifungal classes (enfumafungin and manogepix). Although manogepix is a promising antifungal candidate for candidiasis, resistance mechanisms associated to efflux pump for this antifungal were already reported. To avoid cross-resistance mechanisms, antifungal agents with novel modes of action need to be urgently developed, as arylamidine T-2307 that targets the inhibition of fungal respiratory chain or N-[3-(allyloxy)-phenyl]-4-methoxybenzamide that acts on *Candida* spp. virulence mechanisms.

The current arsenal defines a limited number of fungal targets. A potential means of identifying new targets is to reveal what nature has already determined as effective targets. Natural compounds are an attractive source of antifungal agents with different mechanisms of action. To date, several extracts from plants and microorganisms with antifungal activity were identified; however, discovery, isolation, and interrogation can be a laborious, multifaceted processes. Thus, the challenge is best met by close collaborations between academia and the biotechnology sector.

Seeking to accelerate the introduction of new antifungal treatments into clinical practice, repurposing drugs presents an accelerated track. Drug repurposing has entailed screening a vast number of curated compounds from around the word. Most drugs with antifungal activities were identified among antibacterial, anti-parasitic, and anti-cancer classes. However, drug repurposing can present limitation as well. In some cases, the new use of a compound as an antifungal drug requires higher doses than the original defined use, which can result in adverse effects or toxicity. Therefore, pharmacokinetic aspects such as plasma protein binding, half-life, and tissue distribution need to be carefully evaluated for the new drug dosage and treatment regimen [179,181].

Therapy combinations are also an attractive means to multiply the drug arsenal through different amalgamations simultaneously affect multiple fungal targets, reaching synergistic effects that enhance the antifungal activities, reduce the therapeutic dosage, and impair the development of antifungal resistance. Diverse compounds have demonstrated synergistic action with polyenes, azoles, and echinocandins drugs. Photodynamic therapy offers an additional impact that can be deployed with antifungal therapies as a means to enhance antifungal action on superficial candidiasis. In additional, new nano-particulate drug delivery systems have emerged with advantages to traditional antifungal drug delivery systems such as liposomal, colloidal, and polymeric carriers. Currently, promising nano-particulate carriers primary involve lipidic, polymeric and metal nanoparticles.

In summary, scientists continue to stretch limited resources to their maximum potential but *Candida* spp. fights back by developing new means of resistance. With limited resources, scientists have strategically assembled pharmacotherapeutic options through new compounds, repurposing, combinations, and delivery methods that offer promising future perspectives for candidiasis.

Funding:

The authors acknowledge support from the National Council for Scientific Development (CNPq): through the Researcher on Productivity PQ-1C award granted to JC Junqueira (award no. 306330/2018–0). L Scorzoni has also received a Coordination for the Improvement of Higher Education Personnel (CAPES) scholarship while E Mylonakis and BB Fuchs were supported by NIH grant P20 GM121344.

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Article highlights

- Enchochleated-Amphotericin B (Coch-AmB), tetrazoles, rezafungin, enfumafungin, manogepix and arylamidine are new promising antifungal drugs.
- Drug repurposing using antibacterial, antiviral, and non-antimicrobial drugs can accelerate the introduction of new antifungal agents into clinical practice.
- Drug combinations are attractive options that can enhance the antifungal activities and impair development of antifungal resistance.
- Innovative drug delivery systems for antifungal compounds have been successfully developed using solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), polymeric nanoparticles, and metal-based nanoparticles.
- The success of each antimicrobial agent brings strategic insights to the next phased approach in treating *Candida* spp. infections.

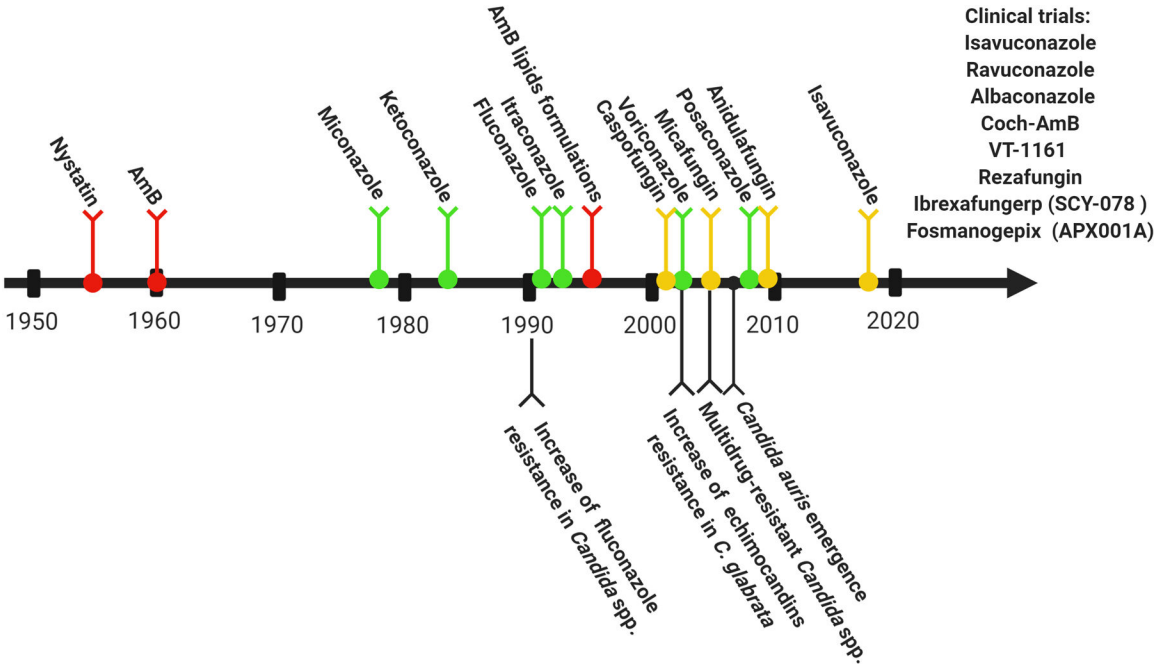

Figure 1:

Timeline of antifungal discovery and emergence of drug-resistant *Candida* isolates. Polyenes are represented in red lines, azoles are represented in green lines and echinocandins are represented in yellow lines. This figure is based on the studies of Ananda-Rajah *el al.* [263], Perlin *et al.* [264] and Alexander *et al.* [265]. Created with BioRender.com.

Table 1.

Resistance index of *Candida* strains to antifungal agents in different countries

Country	Clinical specimen	Resistance index	References
Argentina	Vulvovaginal	Fluconazole (3.55% *C. albicans*)	[227]
Brazil	Saliva and oropharyngeal	Fluconazole (27% *C. albicans*)	[228]
Brazil	blood	Fluconazol (6% *C. glabrata*; 7.3% *C. tropicalis*) Voriconazol (4.9% *C. tropicalis*)	[229]
Canada	blood	Fluconazole (0.6 % *C. albicans*; 1% *C. glabrata*; 4.9% *C. parapsilosis* complex) Micafungin (0.1% *C. albicans*; 2.5% *C. glabrata*)	[230]
China	Invasive candidiasis	Fluconazole (20% *C. albicans*; 11% *C. glabrata*; 29.7% *C. tropicalis*; 20% *C. parapsilosis*) Itraconazole (28.2% C. *albicans*; 6.8% *C. glabrata*; 40.5 % C. *tropicalis*; 33.4% *C. krusei*; 20% *C. parapsilosis*) Voriconazole (23.6% *C. albicans*; 6.8% *C. glabrata*; 27% *C. tropicalis*; 25% *C. krusei;* 20% *C. parapsilosis)*	[231]
Ghana	vulvovaginal	Fluconazole (50% *C. albicans*; 12 % C. *glabrata*; 1% *C. parapsilosis*) Niatatin (4%*C. glabrata*; 1% *C. krusei*) Voriconazole (7% *C. albicans*; 11% *C. glabrata*; 1% *C. krusei*; 1% *C. parapsilosis*)	[232]
Iran	oropharyngeal	ketoconazole (93.75% *C. albicans;* 89.28% of *Candida* non-*albicans Candida* species) Fluconazole (62.50% *C. albicans; 42.85% Candida* non-*albicans Candida* species)	[233]
Ireland	blood	Fluconazole (2% *C. albicans*; 37 % C. *glabrata* Itraconazole (5% *C. albicans*; 21% C. *glabrata*; Flucytosine (3% *C. albicans*) Amphotericin B (14% *C. glabrata*)	[234]
Italy	blood	Fluconazole (1.2% *C. albicans*; 12% C. *glabrata*; 6% *C. parapsilosis,* 10% *C. tropicalis*) Itraconazole (2% *C. albicans*; 25% C. *glabrata*; 0.7% *C. parapsilosis,* 3.9% *C. tropicalis*) Voriconazole (1.4% *C. albicans*; 0.7% *C. parapsilosis,* 1.9% *C. tropicalis*) Anidulafungin (0.5% C. *glabrata*; 1.9% *C. tropicalis*) Caspofungin (0.5% C. *glabrata*; 1.9% *C. tropicalis*)	[235]
Peru	blood	Fluconazole (*C. parapsilosis* 2,3%) Voriconazole (5% *C. albicans*)	[236]
Peru	blood	Fluconazole (2.2% *C. albicans*; 5% *C. parapsilosis*)	[237]
Saudi Arabia	blood	Fluconazole (23% *C. albicans*; 27.8% *C. tropicalis*; 51.7% *C. glabrata*; 48% *C. parapsilosis*) Voriconazole (17% *C. albicans*; 12,5% *C. tropicalis*; 21.7% *C. glabrata*; 2% C. *parapsilosis;* 6% *C. krusei*) Amphotericin B (2% *C. albicans*; 23.5% *C. krusei*) Caspofungin (23% *C. albicans*; 4.2% *C. tropicalis*; 3.3% *C. glabrata*; 6% *C. krusei*)	[238]
Scotland	blood	Fluconazole (5.26% *C. glabrata*)	[239]
Spain	blood	Fluconazole (0.3% *C. albicans*; 6.6% *C. tropicalis*; 10.8% *C. glabrata*; 0.9% *C. parapsilosis*) Voriconazole (6.6% *C. tropicalis*) Caspofungin (0.7% *C. albicans*; 1.08% C. *glabrata*) Micafungin (0.35% *C. albicans*)	[240]
Taiwan	blood	Fluconazole (13.9% *C. tropicalis*; 3.1% *C. glabrata*; 6.1% *C. parapsilosis*) Voriconazole (10.7% *C. tropicalis*) Caspofungina (2.5% *C. tropicalis*; 2.1% C. *glabrata*) Micafungina (2.5% *C. tropicalis*; 5.2% *C. glabrata*) Anidulafungina (1.6% *C. tropicalis*; 5.2% *C. glabrata*)	[241]
Turkey	blood	Fluconazole (2.8 % *C. glabrata*)	[242]
USA	blood	Fluconazole (0.3% *C. albicans*; 8.6% *C. glabrata*; 7.6% *C. parapsilosis;* 4.2% *C. tropicalis*) Voriconazole (0.1% *C. albicans*; 2.1% *C. parapsilosis*; 2.1% *C. tropicalis*) Echinocandins (0.4% *C. albicans*; 4.4% *C. glabrata*; 2.6% *C. krusei*)	[243]

Country	Clinical specimen	Resistance index	References
Pakistan, India, South Africa, and Venezuela	blood, urine, soft tissue and other	Fluconazole (93% *C. auris*) Amphotericin B (35% *C. auris*) Echinocandins (7% *C. auris*) Flucytosine (6% *C. auris*)	[115]
Southern Asian, South African and Japanese/ Korean	Nosocamial infection	Amphotericin B (14.6% *C. auris*) Fluconazole (100% *C. auris*) Itraconazole (4.6% *C. auris*) Voriconazole (48.3% *C. auris*) Posaconazole (12.8% *C. auris*) Isavuconazole (5.9% *C. auris*) Anidulafungin (*C. auris* 6.8%) Nistatina 3.6% (*C. auris*)	[244]
USA	blood, urine and extern ear channel	Fluconazole (71.4% *C. auris*) Voriconazole (14.2 *C. auris*) Amphotericin B (14.2% *C. auris*)	[245]
Spain	Urine and blood	Fluconazole (100% *C. auris*) Voriconazole (17.9% *C. auris*) Isavuconazole (1.8% *C. auris*) Anidulafungin (3.6% *C. auris*)	[246]

Table 2.

Drug repurposing for candidiasis: compounds active against *Candida* spp.; its action on virulence mechanism and combinatory effect with antifungal drugs

Drug classes according to traditional use	Compounds	Antifungal action	Reference
Antibacterial	Sulfa antibacterial drugs	Reverse azole resistance, synergism fluconazole	[183]
	Clotrimazole	Growth inhibition	[189]
	Dequalinium dichloride	Growth inhibition	[189,247]
	Ciclopirox ethanolamine	Growth inhibition	[189,247]
	Nifuroxime	Growth inhibition	[248]
	Nitroxoline	Growth inhibition, anti-biofilm, synergism miconazole	[248,249]
	Chlorquinaldol	Growth inhibition	[248]
	Octanoic Acid	Growth inhibition	[248]
Antiseptics	Thimerosal	Anti-biofilm	[250]
	Benzethonium chloride	Growth inhibition, anti-biofilm	[189,247,250]
	Alexidine dihydrochloride	Growth inhibition, anti-biofilm	[247,250]
	Thonzonium bromide	Growth inhibition, anti-biofilm	[189,247,250]
	Chlorhexidine	Growth inhibition, anti-biofilm	[189,250]
	Methyl benzethonium chloride	Growth inhibition, anti-biofilm	[189,247,250]
	Chloroxine	Growth inhibition anti-biofilm	[189,247,250]
	Monensin sodium salt	Anti-biofilm	[250]
	Clioquinol	Growth inhibition, anti-biofilm	[189,247,250]
	Hexachlorophene	Growth inhibition, anti-biofilm synergism miconazole	[247,249,250]
	Boric acid	Biofilm reduction, growth and germination inhibition	[251]
	Bacitracin	Anti-biofilm	[250]
Disinfectant	Broxyquinoline	Anti-biofilm, synergism miconazole	[249]
Antiviral agent	Ribavirin	Growth inhibition, synergism azole	[189]
	Indinavir	Growth inhibition, aspartyl protease inhibition	[190]
	Ritonavir	Growth inhibition, aspartyl protease inhibition	[190]
Antiparasitic	Pyrvinium pamoate	Growth inhibition, anti-biofilm, anti-biofilm synergism miconazole	[189,247,249,250,252]
	Pentamidine isethionate	Growth inhibition, anti-biofilm, synergism miconazole	[189,252]
	Avermectin B1a	Anti-biofilm	[250]
	Dihydroartemisinin	Growth inhibition, anti-biofilm, synergism miconazole	[247,249]
	Gentian violet	Anti-biofilm, synergism miconazole	[249]
	Bithionate disodium	Anti-biofilm, synergism miconazole	[249]
	Artesunate	Anti-biofilm, synergism miconazole	[249]
	Pinaverium bromide	Growth inhibition	[189]

Drug classes according to traditional use	Compounds	Antifungal action	Reference
	Avermectin B1	Growth inhibition	[189]
	Triclabendazole	Growth inhibition	[189]
Emetic	R(−)-Apomorphine hydrochloride Hemihydrate	Growth inhibition	[252]
Antiemetic	Thiethylperazine dimalate	Growth inhibition	[247]
	Trifluoperazine dihydrochloride	Growth inhibition	[247]
Anti-hypertensive	Amlodipine besilate	Anti-biofilm	[253]
	Guanadrel sulfate	Growth inhibition	[247]
	Nisoldipine	Growth inhibition	[252]
Anestesic	Tramadol	Germ tube formation, adhesion, anti-biofilms	[254]
	Dimethisoquin hydrochloride	Growth inhibition	[247,252]
	Dyclonine hydrochloride	Growth inhibition	[247]
Anticancer	Vinblastine	Anti-biofilm, growth inhibition	[255,256]
	Vincristine	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Paclitaxel	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Docetaxel	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Oxaliplatin	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Carboplatin	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Cisplatin	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Gemcitabine	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Bleomycin	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Doxorubicin	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	5-Fluorouracil	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Decarbazine	Anti-biofilm	[255]
	Etoposide	Anti-biofilm	[255]
	Leucovorin or folinic acid	Anti-biofilm	[255]
	Tamoxifen	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Irinotecan	Anti-biofilm, growth and germ tubes inhibition	[255,256]
	Daunorubicin	Growth and germ tubes inhibition	[256]
	Mitoxantrone	Growth and germ tubes inhibition	[256]
	Mitomycin-C	Growth and germ tubes inhibition	[256]
	Epirubicin	Growth and germ tubes inhibition	[256]
	Dactinomycin	Growth and germ tubes inhibition	[256]
	Busulfan	Growth and germ tubes inhibition	[256]
	Carmustine	Growth and germ tubes inhibition	[256]
	Cyclophosmamide	Growth and germ tubes inhibition	[256]
	Ifosfamide	Growth and germ tubes inhibition	[256]
	Melphalan	Growth and germ tubes inhibition	[256]
	Methotrexate	Growth and germ tubes inhibition	[256]

Drug classes according to traditional use	Compounds	Antifungal action	Reference
	Hydrooxyurea	Growth inhibition	[256]
	Formestane	Growth and germ tubes inhibition	[256]
	Etoposide	Growth and germ tubes inhibition	[256]
	Leuprolide	Growth and germ tubes inhibition	[256]
	Dacarbazine	Growth and germ tubes inhibition	[256]
	Melengestrol acetate	Growth inhibition	[257]
	Megestrol acetate	Growth inhibition	[257]
	Tosedostat	Growth inhibition, morphological changes	[257]
	Amonafide	Growth inhibition, morphological changes	[257]
	Rapamycin	Growth inhibition, morphological changes	[257]
	Thioguanine	Growth inhibition	[189]
	Thiosemicarbazone	Growth inhibition, azole synergism	[196]
Antipsychotic	Methiothepin maleate	Growth inhibition	[247,257]
	Haloperidol	Growth inhibition, morphological changes	[257]
	Trifluperidol 2HCl	Growth inhibition, morphological changes	[257]
	Bromperidol and derivates	Growth inhibition, azole synergism	[258]
	Zotepine	Growth inhibition, anti-biofilm	[247,250]
	Prochlorperazine dimaleate	Growth inhibition	[247]
Antiepileptic/ Antidepressant	Diazepam	Growth and germ tubes inhibition, anti-biofilm	[259]
	Lorazepam	Growth and germ tubes inhibition, anti-biofilm	[259]
	Midazolam	Growth and germ tubes inhibition, anti-biofilm	[259]
	Phenobarbitone	Growth and germ tubes inhibition and anti-biofilm	[259]
	Tamoxifen citrate	Growth inhibition	[247,257]
	Sertraline	Growth inhibition, morphological changes and anti-biofilm	[197,247]
	Rolipram	Growth inhibition	[247]
Anemia	Stanozolol	Growth inhibition	[257]
Anti-inflammatory	Ebselen	Synergism fluconazole/anidulafungin, anti-biofilm	[247,252]
Anticoagulant	Argatroban	Growth inhibition	[252]
Antipsoriatic	Anthralin	Growth inhibition	[189]
Antihyperlipidemic	Fluvastatin	Growth inhibition	[248]
Anti-fadigue	Fipexide hydrochloride	Growth inhibition	[247]
Antirheumatic/ analgesic	Auranofin	Growth inhibition, anti-biofilm	[185,189,250,257,260]
Antilipemic	Tetra ethylenepentamine pentahydrochloride	Growth inhibition	[189]
Broad spectrum of pharmacologic effects	Pilocarpine	Morphological changes and anti-biofilm	[261]
Benign prostatic hyperplasia	Finasteride	Morphological changes anti-biofilm and synergism fluconazole	[262]
Chelating agent	Pentetic acid	Growth inhibition	[189,252]

Drug classes according to traditional use	Compounds	Antifungal action	Reference
Coronary dilator, spasmolytic, uricosuric	Benzbromarone	Anti-biofilm	[250]
Decongestant	Octodrine	Growth inhibition	[248]
Deterrent of alcohol consumption	Disulfiram	Growth inhibition	[189,248,257]
Immune-suppression	Mycophenolic acid	Growth inhibition	[248]
Mydriatic vasodilator	Yohimbine hydrochloride	Anti-biofilm	[250]
Vasodilator/Antiplatelet	Suloctidil	Growth inhibition, voriconazole synergism	[247,252]