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MINI-REVIEW

Drug repurposing strategies in the development of potential antifungal agents

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Abstract

The morbidity and mortality caused by invasive fungal infections are increasing across the globe due to developments in transplant surgery, the use of immunosuppressive agents, and the emergence of drug-resistant fungal strains, which has led to a challenge in terms of treatment due to the limitations of three classes of drugs. Hence, it is imperative to establish effective strategies to identify and design new antifungal drugs. Drug repurposing is a potential way of expanding the application of existing drugs. Recently, various existing drugs have been shown to be useful in the prevention and treatment of invasive fungi. In this review, we summarize the currently used antifungal agents. In addition, the most up-to-date information on the effectiveness of existing drugs with antifungal activity is discussed. Moreover, the antifungal mechanisms of existing drugs are highlighted. These data will provide valuable knowledge to stimulate further investigation and clinical application in this field.

Key points

- *Conventional antifungal agents have limitations due to the occurrence of drug-resistant strains.*
- *Non-antifungal drugs act as antifungal agents in various ways toward different targets.*
- *Non-antifungal drugs with antifungal activity are demonstrated as effective antifungal strategies.*

Keywords Drug repurposing · Antifungal therapy · Antifungal mechanism · Clinical application · Antifungal agent

Introduction

Fungal infection has become a significant event leading to over 1.5 million deaths annually worldwide (Deaguero et al. 2020). To date, the most common fungal infections related to human mortality and morbidity are caused by *Cryptococcus*, *Candida*, and *Aspergillus* (Boral et al. 2018). The impact of mycoses has increased, especially in patients with immunodeficiency disorders who have undergone transplant surgery, chemoradiotherapy, hemodialysis, or the treatment with immunosuppressive agents (Drgona et al. 2014). Hence, antifungal therapy represents a challenging problem for clinicians. In addition, the limited number of antifungal agents in the clinic can induce side effects and a great number of drug-resistant or multidrug-resistant strains have emerged. *Candida auris*, a multidrug-resistant fungus, has shown a global increase in recent years. Importantly, some of these infections are resistant to almost all current antifungal agents (Du et al. 2020). In

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New Delhi, it was reported that 15 COVID-19 patients had secondary candidiasis in the intensive care unit (ICU), two-thirds of which were caused by *C. auris*, and the mortality rate was up to 60 % (Chowdhary et al. 2020). *Lomentospora prolificans* is another classic fungus with intrinsic resistance to nearly all existing antifungal agents (Pellon et al. 2018). In *A. fumigatus*, the emergence of azole resistance has made the treatment of aspergillosis a global public health problem, especially in Australia, China, the USA, and parts of Europe (Meis et al. 2016). More than 25 % of *A. fumigatus* has been found to be resistant to the triazole antifungal agents in an ICU in the Netherlands (Lestrade et al. 2016). More concerningly, patients with invasive aspergillosis caused by azole-resistant *A. fumigatus* have mortality rates ranging from 50 to 100 % (Lestrade et al. 2019).

Currently, the first-line antifungal agents for invasive fungal infections are amphotericin B, echinocandins, isavuconazole, itraconazole, posaconazole, and voriconazole (Zhao et al. 2016). However, due to the existence of toxicity and drug-resistant strains, the present antifungal options have become more restricted. A variety of approaches have been employed to conduct antifungal therapies, such as the synthesis of new substances, the use of extracts from organisms, changing of the administration methods or forms of old drugs to treat fungal diseases, and an association between known antifungal drugs and non-antifungal agents (Robbins et al. 2016). Moreover, drug repurposing is a potential strategy for the treatment of invasive fungal infections, owing to the excellent antifungal activity of these drugs. Several agents have recently been confirmed to serve as antifungal candidates in the treatment of mycoses. The purpose of this review is to present a series of known drugs that have been investigated for their application in the treatment of fungal infections. Firstly, the strategies, mechanisms, and challenges of current antifungal drugs are described. Secondly, the extensive application and antifungal mechanisms of drugs with antifungal activity that is used in the clinic to treat non-mycotic infections are highlighted.

Current antifungal drugs used in clinics

Since the first active antimycotic griseofulvin was recognized in 1939, a multitude of antifungal agents have been used clinically. Polyenes, azoles, echinocandins, and flucytosine are currently the main treatments for invasive fungal infections in clinical settings. In fungi, ergosterol, located in the cell membrane, regulates membrane structure permeability, mobility, and substance transportation by making direct linkages with the phospholipid membrane (Anderson et al. 2014). The representative polyene drug is amphotericin B, which can bind to ergosterol from lipid bilayers and form large and extramembranous aggregates (Anderson et al. 2014). These extramembranous aggregates lead to the formation of transmembranal pores, which can leak cellular components. This results in the death of pathogenic fungi (Anderson et al. 2014). As the "gold standard" for combating invasive fungal infections for decades, amphotericin B has a relatively broad spectrum of antifungal activity against yeasts and molds (Ostrosky-Zeichner et al. 2003). For instance, an investigation of 78 *Candida* sp. clinical strains showed that all examined free-living cells were susceptible to amphotericin B (Prazynska and Gospodarek 2014). The MIC_{90} of amphotericin B for common yeasts in clinical settings ranges from 0.25 to 2 μg/mL and is 1–4 μg/mL for clinically important molds (Ellis 2002). In addition, amphotericin B has been used as an alternative therapy for invasive aspergillosis (Patterson et al. 2016). In vitro, amphotericin B combined with caspofungin and voriconazole has synergistic anti-*Aspergillus* species effects (O'Shaughnessy et al. 2006), but these findings have not been validated in vivo (Baddley and Pappas 2005; Haidar and Singh 2018). Moreover, the clinical applications of amphotericin B have been limited due to toxicity, which includes nephrotoxicity and infusion-related reactions such as chest pain, dyspnea, hypoxia, flushing, and urticaria (Roden et al. 2003). To resolve this problem, lipid formations of amphotericin B, including liposomal amphotericin B (LAmB), AmpB lipid complex (ABLC), and AmpB colloid dispersion (ABCD), were developed (Ostrosky-Zeichner et al. 2003). Toxicity was greatly reduced using these formulations; however, they are inefficient in penetrating certain tissues, such as the kidney, and thus fail to reach therapeutic concentrations (Smitherman 2016).

Due to the safety and wide availability, azoles (including fluconazole, isavuconazole, itraconazole, posaconazole, and voriconazole) are the most widely used antifungal agents. Azoles can be used against the majority of fungi, as they inhibit the cytochrome P450-dependent enzyme 14α demethylase (Cyp51) (Emami et al. 2017). Lanosterol conversion into ergosterol is blocked when azoles inhibit Cyp51. Azoles have excellent therapeutic effects on molds as well as yeasts (Meis et al. 2016; Patterson et al. 2016; Robbins et al. 2017). For example, in a randomized trial, voriconazole was used in therapy for invasive aspergillosis and achieved a 52.8 % curative rate (Haidar and Singh 2018). However, the extensive use of azoles has subsequently led to the emergence of acquired azole resistance, particularly in *Aspergillus* species (Wiederhold 2017). A resistance rate of 26 % was found in *A. fumigatus* culture–positive patients in the ICU (Paassen et al. 2016). Azoles can also bind to the human cytochrome P450 enzyme system (CYP450), leading to reduced antifungal efficiency (Wiederhold 2018).

Echinocandins are a group of effective antifungal agents which, according to the current Infectious Society of America (IDSA) and European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) guidelines,

are useful for the primary treatment of invasive candidiasis (Chang et al. 2017). Anidulafungin, caspofungin, and micafungin are representatives of this group (Emri et al. 2013). Compared with the azole antifungal agents, echinocandins rarely cause resistance, have a good safety profile, have better clinical outcomes, and have been used for two decades. The mechanism of echinocandins mainly involves inhibition of cell wall synthesis by inhibiting β-1,3-D-glucan synthase, a key cell wall component of pathogenic fungi. Following treatment with echinocandins, the buried glucan cell wall architecture can be exposed, which induces abnormal morphology and growth limitation. The time-kill methodology of *C. albicans* biofilms, treated with caspofungin, displayed at least 99 % killing at physiological concentrations. Investigations in AIDS patients, who were unable to tolerate amphotericin B, have also shown that caspofungin is an efficient therapeutic option for azole-resistant *Candida* infections (Ramage et al. 2002; Garbino 2004). Anidulafungin is an excellent therapeutic choice against *Aspergillus* and *Candida* species, including those resistant to either fluconazole or amphotericin B. A literature review mentioned that it was a superior option to fluconazole in the treatment of oesophageal candidiasis and candidemia (Vazquez 2005). Micafungin also exhibits excellent activity on *Candida* spp. resistant to multiple azoles, and 8 μg/mL of micafungin demonstrated a 57 % antifungal rate in *C. parapsilosis* (Gil-Alonso et al. 2015). Nevertheless, probably due to the differences in cell wall composition or structure, this class is largely inactive in most filamentous fungi including Zygomycetes and *Fusarium* species (Perlin 2020). In addition, *C. neoformans* is naturally resistant to echinocandins, which are completely ineffective in treating cryptococcosis (Denning 2003). Additionally, due to their characteristic large molecular weight, low oral bioavailability, and limited absorption in the gastrointestinal tract, these drugs are only administered intravenously.

Flucytosine is also an important antifungal agent that inhibits the synthesis of DNA and RNA and is mainly used to treat cryptococcosis and candidiasis (Bennet 1977). Because of the poor efficacy of monotherapy due to the prevalence of intrinsically resistant strains (approximately 10 % *C. albicans* isolates) and the frequent development of resistance during treatment (Vermes et al. 2000), flucytosine is always used in combination with another antifungal agent (such as amphotericin B). These combination treatments have shown promising clinical effects. For example, 49 HIV-infected patients with cryptococcosis treated with combination flucytosine and amphotericin B were reported to have a higher survival rate than patients receiving amphotericin B alone (Chuck and Sande 1989). For candidiasis, several similar trials have shown that this combined regimen also has synergic activity against a variety of *Candida* spp. (Medoff et al. 1971; Montgomerie et al. 1975; Smego Jr et al. 1984). Currently, flucytosine combined with amphotericin B is the standard induction therapy for *Cryptococcal* and *Candida* meningitis, because it has lower rates of treatment failure and mortality than other alternative approaches (Bridges et al. 2017; Greene et al. 2020).

Azole resistance among *Candida* species, such as *C. auris* and *Aspergillus* species, as well as echinocandin resistance in *C. glabrata* is an alarming problem (Wiederhold 2017). In addition, other molds such as *Scedosporium* and *Fusarium* species have reduced susceptibility to clinically available antifungal drugs (Wiederhold 2017). Although amphotericin B is recognized to have excellent antifungal activity, there are still fungi, such as *C. lusitaniae* and *A. terreus* that show intrinsic resistance to amphotericin B (Arendrup et al. 2012). Consequently, the development of new antifungals is needed to resolve this issue.

Drug repurposing strategy

Compared with the development of new drugs, drug repurposing has several advantages, as mainly reflected in decreased cost and security risk (Cha et al. 2018). The average new drug development time savings has been estimated to reach 5–7 years, and the failure rate for problems related to safety or toxicity is less than 50 % (Ashburn and Thor 2004). Drug repurposing involves tapping into new applications for existing drugs and thus requires an innovative clinical in-depth investigation of the pharmacological mechanisms. For example, aspirin, a traditional drug with analgesic and antipyretic activity initially, and is now gradually being used in the prevention and treatment of multi-system diseases including cardiovascular disease, stroke, and digestive tract cancers (Theken and Grosser 2018; Bosetti et al. 2020; Burn et al. 2020; Johnston et al. 2020). Vitamin D is widely used to regulate calcium and phosphate metabolism for bone health (Ng et al. 2019). Recent studies have found that vitamin D deficiency is associated with an increased risk of cardiovascular disease, diabetes, hypercholesterolemia, and even COVID-19 (Kouvari et al. 2020; Meltzer et al. 2020). Metformin, originally used to treat diabetes, has so far more than a dozen potential new functions including the treatment and prevention of cancer, cardiovascular disease, and mental illness such as infantile autism and cognitive disorder (Tseng 2015; Dy et al. 2018; Shiers et al. 2018; Arrieta et al. 2019; Cheung et al. 2019; Lee et al. 2019; Mohan et al. 2019).

In addition, drug repurposing is also very significant in the development of new antifungal drugs, the effectiveness of existing drugs with antifungal activity have been associated with exciting non-antifungal agents chiefly consisting of antibacterial drugs, immunosuppressants, statins, antiarrhythmic drugs, antipsychotic drugs, antidepressant drugs, and non-steroidal anti-inflammatory drugs (NSAIDs).

Antibacterial drugs

The discovery of antibacterial drugs has been the greatest invention of medical science in reducing morbidity and mortality. Traditionally, antibacterial drugs were commonly used as medical treatments for infectious diseases caused by gram-negative bacteria, gram-positive bacteria, mycoplasma, chlamydia, rickettsia, as well as spirochaetes. Antibacterial drugs with antifungal activity mainly include tetracyclines (e.g., demeclocycline, doxycycline, minocycline, and tigecycline), aminoglycosides (e.g., gentamicin, neomycin, paromomycin, ribostamycin, streptomycin, and tobramycin), macrolides (e.g., azithromycin and clarithromycin), quinolone polypeptides (e.g., ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, and trovafloxacin), polypeptides (e.g., polymyxin B), and others such as linezolid and rifampicin. Many studies in vitro and in animal models have revealed that antibacterial drugs have broad-spectrum antifungal activity (Table 1). In general, they are commonly used alone or in combination to regulate the gene expression levels of adhesion, hypha, or biofilm formation, to decrease extracellular glycan level and cell surface hydrophobicity, and even to inhibit efflux pump activity. In *Fusarium* spp., tobramycin combined with amphotericin B and voriconazole has an 80 % and 76 % synergistic effect, respectively, in increasing the permeability of the cell wall and cell membrane (Venturini et al. 2016). Minocycline, a tetracycline, has been verified to exhibit broad-spectrum antifungal activity against *A. fumigatus*, *A. flavus*, *Fusarium solani*, and *F. oxysporum* with MICs in the range of 0.125–4 μg/mL. In addition, a series of studies on the antifungal activity of minocycline combined with antifungal agents (amphotericin B, fluconazole, itraconazole, posaconazole, and voriconazole) have been reported (Lew et al. 1977; Shi et al. 2010; Loreto et al. 2014; Gao et al. 2020). Similar findings have also been confirmed for polymyxin B which mainly combines with ketoconazole, micafungin, and amphotericin B in *C. albicans* to alter the permeability of the cell membrane (Moneib 1995). Moreover, polymyxin B can bind anionic lipids on the fungal membrane, both alone, with the MIC_{100} range from 8 to 256 μg/mL, and combined with fluconazole for *Fusarium* spp., *C. neoformans*, *Rhizopus oryzae*, and *A. fumigatus*, which destroys the membrane integrity (Zhai et al. 2010; Venturini et al. 2016). Many animal models have also been used to verify the antifungal activity of antibacterial agents. In the murine model of candidiasis, a combination of cefoperazone–sulbactam, colistin, or meropenem with caspofungin has been found to result in lower fungal burden in the kidneys, than that after treatment with caspofungin alone (Ozcan et al. 2006; Zeidler et al. 2013; Keçeli et al. 2014). Histopathological results indicated that the degree of inflammation was 25 % less in the group treated with caspofungin and meropenem than caspofungin monotherapy (Ozcan et al. 2006). In mice, quinolones combined with fluconazole and amphotericin B also have synergistic effects against invasive candidiasis (Sugar et al. 1997; Sasaki et al. 2000). β-Lactam derivatives show broad-spectrum antifungal activity in vitro against *Candida* spp. and *Aspergillus* spp. (Gowri et al. 2016; O'Driscoll et al. 2008; Mohamadzadeh et al. 2020). However, studies have indicated that β-lactam antibiotics are unable to inhibit the growth of *Candida* species, and amoxicillin can increase the virulence of *Candida krusei* and *Candida tropicalis* in *Caenorhabditis elegans* (Aguiar Cordeiro et al. 2018).

Biofilms represent one of the major virulence factors in pathogenic fungi, which develop on the surfaces of stents, shunts, prostheses, implants, endotracheal tubes, pacemakers, and various types of catheters (Sardi Jde et al. 2014). Compared to planktonic cells, the interior biofilm cells display severe resistance to a wide variety of clinical antifungal agents. A small subset of yeast cells in *C. albicans* biofilms were found to be highly resistant to amphotericin B. This resistance was independent of the upregulation of efflux pumps and cell membrane composition (Sardi Jde et al. 2014). When combined with clarithromycin, the permeability barrier of the biofilm matrix was altered, which resulted in increased penetration of amphotericin B (Del Pozo et al. 2011). In addition, doxycycline, tigecycline, and rifampicin were also found to enhance the activity of amphotericin B to suppress biofilm formation (Lew et al. 1977; El-Azizi 2007; Miceli et al. 2009; Ku et al. 2010; Del Pozo et al. 2011; Venturini et al. 2016; Fernández-Rivero et al. 2017).

Thus, antibacterial drugs have potential antifungal value due to their good antifungal activity. However, human health is based on the balance of microbiota (Limon et al. 2017; Liu et al. 2020). If antibacterial drugs are approved for the treatment of invasive fungal infections, many problems still need to be considered. For instance, antibiotic treatment will reduce the composition of colonizing microbiota (Sam et al. 2017). Moreover, many antimicrobial drugs can promote fungal growth and enhance fungal pathogenicity indirectly by disrupting the microbiome and eliminating anaerobic bacteria, which might inhibit fungi, especially in the gut (Sam et al. 2017). Our previous investigation (unpublished article) also showed that the antifungal applications of antibiotics interfere with the homeostasis of symbiotic bacteria and fungi in the body. Moreover, dysbiosis of microbiota is responsible for the occurrence of many other diseases in humans such as cardiovascular, cancer, allergy, and the microbiota also affect the human immune system and the synthesis of nutrients (Thomas et al. 2017; Ran et al. 2020). In addition, the pharmacokinetics of antibiotics with antifungal activity in vivo require further investigation.

Table 1 Summary of antibacterial drugs with antifungal activity

Antibiotics	Fungus	In vitro (MIC: μg/mL)	In vivo	In combination (synergistic effects)	Relevant molecular mechanism	Ref.
Tobramycin	*Fusarium* spp.	> 64	-	VRC, AmB	Probably increases permeability of the cell wall and cell membrane.	Venturini et al. (2016)
Gentamicin	Resistant-azole *C. albicans*	> 512	*G. mellonella*	FLC	(I) Suppresses overexpression of the efflux pump. (II) Reduces phospholipase activity of resistant *C. albicans*.	Lu et al. (2018)
Clarithromycin	*C. tropicalis*	-	-	AmB, ANI	-	Fernández-Rivero et al. (2017)
	C. parapsilosis, C. glabrata, C. albicans	No effects	-	AmB	-	Del Pozo et al. (2011)
	Pythium insidiosum	0.25–8	-	-	-	Loreto et al. (2014)
Azithromycin	*Pythium insidiosum*	1–16	-	-	-	Loreto et al. (2014)
	Aspergillus spp.	No effects	-	AmB	Probably inhibits mitochondrial protein synthesis.	Nguyen et al. (1997)
Norfloxacin	*C. albicans*	-	-	MIA	-	Moneib (1995)
Levofloxacin	*C. albicans, A. fumigatus*	+	-	AmB, CAS	Probably inhibits fungal DNA replication by binding to fungal topoisomerase.	Stergiopoulou et al. (2009)
Gatifloxacin	*Candida* spp.	+	-	-	-	Ozdek et al. (2006)
Moxifloxacin	*C. albicans*	+	-	Liposomal AmB, CAS	Probably inhibits fungal DNA replication by binding to fungal topoisomerase.	Ozdek et al. (2006); Stergiopoulou et al. (2009); Deren et al. (2010)
Ciprofloxacin	*C. albicans*	+	-	AmB	Probably inhibits fungal DNA replication by binding to *C. albicans* topoisomerase.	Stergiopoulou et al. (2009)
	A. fumigatus	+	-	AmB, CAS, ARC		
Trovafloxacin	*C. albicans*	No effects	Murine	FLC, AmB	-	Sugar et al. (1997)
	C. tropicalis, C. neoformans	No effects	-	FLC, AmB		
Tetracycline	*C. albicans*	320–2560	*G. mellonella*	AmB, FLC	-	Lew et al. (1977); Gu et al. (2018)
Demeclocycline	*C. albicans*	640	-	AmB	-	Lew et al. (1977)
Doxycycline	*C. parapsilosis, C. krusei, C. glabrata*	No effects	-	AmB	Probably inhibits protein synthesis.	El-Azizi (2007)
	C. albicans	640–1280	*G. mellonella*	AmB, FLC, CAS	(I) Inhibits FLC-inducible efflux pump gene overexpression. (II) Disturbs calcium homeostasis. (III) Disturbs iron homeostasis.	Lew et al. (1977); Miceli et al. (2009); Fiori and Van Dijck (2012); Gao et al. (2013); Gao et al. (2014); Gu et al. (2018)
Minocycline	Resistant-FLC *C. albicans*	256–512	-	AmB, FLC	Disturbs calcium homeostasis.	Lew et al. (1977); Shi et al. (2010)
	A. fumigatus	0.125–4	*G. mellonella*	ITR, VRC, POS	Probably interferes with the balance of cellular electrolytes and loss of mitochondrial function.	Loreto et al. (2014); Gao et al. (2020)
	A. flavus, F. solani, F. oxysporum	0.125–4	-	ITR, VRC, POS		

Table 1 (continued)

Antibiotics	Fungus	In vitro (MIC: μg/mL)	In vivo	In combination (synergistic effects)	Relevant molecular mechanism	Ref.
Tigecycline	*C. albicans*	2048	-	AmB, FLC, CAS	-	Ku et al. (2010)
	Fusarium spp.	0.25–4	-	VRC, AmB	Inhibits the synthesis of protein.	Loreto et al. (2014); Venturini et al. (2016)
Polymyxin B	*C. albicans*	-	-	AmB, KET, MIA	Probably alters cell membrane permeability.	Moneib (1995)
	Fusarium spp.	4–16	-	VRC, AmB	Probably disturbs the synthesis of ergosterol.	Venturini et al. (2016)
	C. neoformans	8–256	-	FLC	Probably through binding anionic lipids on fungal membrane and destroys membrane integrity.	Zhai et al. (2010)
	Rhizopus oryzae	32	-	-		
	A. fumigatus	28–56	-	-		
Rifampicin	*C. tropicalis*	-	-	AmB, ANI	-	Fernández-Rivero et al. (2017)
	C. parapsilosis, C. glabrata, C. albicans, C. krusei	No effects	-	AmB	Probably disturbs RNA synthesis in the presence of AmB.	El-Azizi (2007); Loreto et al. (2014)
Linezolid	*Pythium insidiosum*	1–32	-	-	Inhibits protein synthesis.	Loreto et al. (2014)
	C. neoformans	> 64	-	AmB	-	Rossato et al. (2015)
	C. albicans	> 512	*G. mellonella*	FLC, ITR, VRC	Probably inhibits mitochondrial protein synthesis and interferes with the induction of stress-response mitochondrial chaperones.	Lu et al. (2019)

Note: *VRC*, voriconazole; *AmB*, amphotericin B; *FLC*, fluconazole; *ITR*, itraconazole; *CTZ*, clotrimazole; *POS*, posaconazole; *ANI*, anidulafungin; *MIA*, micafungin; *CAS*, caspofungin; *KET*, ketoconazole; -, no studies were mentioned in the corresponding references; +, the drug has antifungal effect, but no specific data in the corresponding references

Table 2 Summary of immunosuppressant drugs with antifungal activity

Immunosuppressants	Fungus	In vitro (MIC: μg/mL)	In vivo	In combination (synergistic effects)	Relevant molecular mechanism	Ref.
Cyclosporine	*Aspergillus* spp.	1–25	-	CAS, ISA	Inhibits the calcineurin pathways.	Marchetti et al. (2000a, 2000b); Kontoyiannis et al. (2003)
	C. albicans	>10	Rat	FLC, VRC, CAS, AmB	Inhibits the expression of genes related to hyphal development, adhesion, biofilm formation, and drug transporter in *C. albicans* (Jia et al. 2016).	Uppuluri et al. (2008); Shinde et al. (2012)
	Rhizopus spp., *Lichtheimia* spp., *Mucor* spp., *Rhizomucor* spp.	1–16	-	ISA		Schwarz et al. (2019)
Tacrolimus	*Trichosporon asahii*	> 64	-	AmB, CAS	Inhibits the activity of calcineurin pathway.	Kubiça et al. (2016)
	Aspergillus spp.	0.25–16	Mice	CAS		High and Washburn (1997); Steinbach et al. (2004); Kubiça et al. (2016); Schwarz and Dannaoui (2020)
	Fusarium spp.	1–40	-	CAS		Shalit et al. (2009)
	C. albicans	No effects.	-	FLC, ITR, VRC		Uppuluri et al. (2008); Sun et al. (2008)
	C. dubliniensis	> 4	-	CAS, FLC, POS		Zhang et al. (2012)
	Rhizopus spp., *Lichtheimia* spp., *Mucor* spp., *Rhizomucor* spp.	1–8	-	ISA		Schwarz et al. (2019)
Pimecrolimus	*Malassezia* spp.	16–64	-	-	-	Sugita et al. (2006)
Rapamycin	*C. albicans*	< 0.09 - > 100	-	-	Inhibits the TOR pathways via FKBP12-Rapa complex.	Cruz et al. (2001)
	C. neoformans	0.39 - >100	-	-		Cruz et al. (2001)
	Mucor spp.	8	*G.mellonella*	ISA		Bastidas et al. 2012; Schwarz et al. (2019)
	Rhizopus spp., *Lichtheimia* spp., *Rhizomucor spp.*	8		ISA		Schwarz et al. (2019)
	Phycomyces blakesleeanus	6.3-200	-	CAS, ISA		Bastidas et al. (2012)
	Aspergillus spp.	16	Mice	ISA		High and Washburn (1997); Kontoyiannis et al. (2003); Schwarz and Dannaoui (2020)
Mycophenolic acid	*C. neoformans*	30	Nematode	AmB	Disrupts *de novo* GTP biosynthesis.	Morrow et al. (2012); Banerjee et al. (2014)
	C. albicans	0.25	-	-		Köhler et al. (2005)
Mizoribine	*C. albicans*	-	-	-	Disrupt *de novo* GTP biosynthesis.	Köhler et al. (2005)

Table 2 (continued)

	Fungus	In vitro (MIC: μg/mL)	In vivo	In combination (synergistic effects)	Relevant molecular mechanism	Ref.
Immunosuppressants						
Dexamethasone	Resistant-azole *C. albicans*	No effects.	*G. mellonella*	FLC	Inhibits the drug efflux pump and reduces the activity of extracellular phospholipases.	Sun et al. (2017)
Budesonide	Resistant-azole *C. albicans*	16- > 128	*G. mellonella*	FLC	(I) Inhibits the function of drug transporters. (II) Reduces the activity of extracellular phospholipases and the formation of biofilm. (III) Promotes apoptosis by the accumulation of ROS.	Li et al. (2016)
Hydrocortisone	*A. fumigatus*	-	-	ITR	-	Ramondenc et al. (1998)

Note: *VRC*, voriconazole; *AmB*, amphotericin B; *FLC*, fluconazole; *ITR*, itraconazole; *POS*, posaconazole; *CAS*, caspofungin; *ISA*, isavuconazole; -, no studies were mentioned in the corresponding references

Immunosuppressants

Immunosuppressants are another example of drug repurposing due to their antifungal activity. It is known that immunosuppressants mainly include calcineurin inhibitors (e.g., cyclosporine; pimecrolimus; and tacrolimus, FK506), target of rapamycin inhibitors (e.g., rapamycin), antimetabolic agents (e.g., mizoribine, MZP; mycophenolic acid, MPA), and glucocorticoids (e.g., budesonide, dexamethasone, and hydrocortisone). Initially, rapamycin was found to be an antifungal agent and inhibited yeasts including *C. albicans*, dermatophytes, *Microsporum gypseum*, and *Trichophyton granulosum* (Vézina et al. 1975). Rapamycin, probably acting on the recombinant FK506 binding protein (FKBP) complex, showed activity on clinical isolates of *Candida* in vitro, on the basis of a randomized controlled trial of rapamycin versus candicidin, nystatin, and amphotericin B. The results demonstrated that rapamycin has antifungal activity superior to that of the other tested compounds (Sehgal et al. 1975). The immunosuppressants found to have antifungal ability are briefly summarized in Table 2.

Inosine monophosphate dehydrogenase (IMPDH) is a crucial enzyme in de novo guanine nucleotide biosynthesis and plays an important role in the rapid proliferation of cells (Cuny et al. 2017). A recent investigation found that benzo[b]thiophene 1,1-dioxide, an IMPDH inhibitor, can weaken the virulence of *C. neoformans* or kill it entirely (Kummari et al. 2018). In addition, MPA and MZP, other types of IMPDH inhibitors, were confirmed to have significant antifungal effects in *C. albicans* and *C. neoformans* by disrupting de novo GTP biosynthesis (Köhler et al. 2005; Morrow et al. 2012; Banerjee et al. 2014). Ribavirin, an antiviral agent, is also a type of IMPDA inhibitor. Interestingly, it was found that ribavirin displayed potent antifungal activity in *C. albicans* in monotherapy or in combination with fluconazole, itraconazole, and posaconazole in vitro and in vivo. The antifungal mechanism involves disruption of vacuolar function and the reduction of extracellular phospholipase activity (Yousfi et al. 2019; Zhang et al. 2020).

Calcineurin, a conserved serine-threonine specific phosphatase, consists of a catalytic subunit and a regulatory subunit (Bandyopadhyay et al. 2004; Sun et al. 2016). It is one of the important mediators in calcium signals and is involved in hyphal/mycelium formation in *C. neoformans* and *A. fumigatus*, and virulence in *C. tropicalis* (Zhang et al. 2012; Chen et al. 2014). Calcineurin inhibitors (cyclosporin A and FK506) have been shown to improve the survival of mice infected with *A. fumigatus* (High and Washburn 1997). Clinical experience has also suggested that calcineurin inhibitors (cyclosporin A and FK506) can decrease the mortality of invasive *Aspergillosis* by forming protein-drug complexes (Torre-Cisneros et al. 1991; Singh et al. 2003). Moreover, cyclosporin A and FK506 combined with fluconazole have

Table 3 Summary of statin drugs with antifungal activity

Statins	Fungus	In vitro (MIC: μg/mL)	In vivo	In combination (synergistic effects)	Relevant molecular mechanism	Ref.
Lovastatin	*Paecilomyces variotii*	64	-	-	-	Chamilos et al. (2006); Nyilasi et al. (2010); Zhou et al. (2018)
	Rhizopus oryzae	128	-	-	-	
	C. albicans	50–64	-	FLC, ITR	Inhibits ergosterol synthesis.	
	C. glabrata	128	-	FLC	-	
	A. fumigatus	25	-	FLC	-	
	Zygomycetes	32–56	-	VRC	-	
Simvastatin	*C. glabrata*	16–32	-	-	(I) Inhibits ergosterol synthesis; (II) Causes the loss of mtDNA.	Chamilos et al. (2006); Nyilasi et al. (2010); Westermeyer and Macreadie (2007)
	C. albicans	8	-	MIA	-	Nyilasi et al. (2010)
	C. utilis	200	-	MIA	Inhibits ergosterol synthesis.	Cabral et al. (2013)
	Cryptococcus spp.	62.5–1000	-	AmB, ITR, FLC	Inhibits ergosterol synthesis.	Silva et al. (2020)
	Saccharomyces cerevisiae	40	-	CTZ, ITR, MIA	Inhibits ergosterol synthesis.	Cabral et al. (2013)
	Paecilomyces variotii	8	-	-	-	Nyilasi et al. (2010)
	Rhizopus oryzae	64	-	-	-	Nyilasi et al. (2010)
	A. fumigatus	6.25	-	FLC	-	Nyilasi et al. (2010)
Pravastatin	*C. albicans*	No effects.	Mice	FLC	Inhibits farnesol production.	Nash et al. (2002)
Atorvastatin	*C. albicans*	16–256	*G. mellonella*	MIA	Inhibits ergosterol synthesis.	Nyilasi et al. (2010); Ajdidi et al. (2019); Esfahani et al. (2019)
	C. glabrata	4–64	-	FLC	-	Nyilasi et al. (2010); Esfahani et al. (2019); Lima et al. (2019)
	C. utilis	200	-	-	-	Silva et al. (2020)
	C. krusei	8	-	-	-	Esfahani et al. (2019)
	C. kefyr	4-16	-	-	-	Esfahani et al. (2019)
	Cryptococcus gattii	≥ 256	Mice	FLC	(I) Inhibits ergosterol synthesis; (II) Induces the production of ROS.	Chin et al. (1997); Ribeiro et al. (2017)
	Saccharomyces cerevisiae	40	-	CTZ, ITR, MIA	-	Cabral et al. (2013)
	C. stellatoidea	16	-	-	-	Esfahani et al. (2019)
	Rhizopus oryzae	32	-	ITR, KET	-	Nyilasi et al. (2010)
	Paecilomyces variotii	32	-	-	-	Nyilasi et al. (2010)
	Aspergillus flavus	> 128	-	ITR	-	Nyilasi et al. (2010)
	A. fumigatus	64	-	ITR, FLC, MIA, KET	(I) Stimulates oxidative stress response; (II) Inhibits ergosterol synthesis.	Nyilasi et al. (2010; Ajdidi et al. (2020)
Fluvastatin	*C. albicans*	25	No effects in mice	FLC	-	Nyilasi et al. (2010); Lima et al. (2019)

Table 3 (continued)

Statins	Fungus	In vitro (MIC: μg/mL)	In vivo	In combination (synergistic effects)	Relevant molecular mechanism	Ref.
	C. glabrata	32–64	-	-	-	Nyilasi et al. (2010); Lima et al. (2019)
	C. tropicalis	128	-	-	-	Lima et al. (2019)
	C. dubliniensis	16–512	-	-	-	Lima et al. (2019)
	Cryptococcus spp.	64- >128	-	ITR, FLC	-	Chin et al. (1997)
	Paecilomyces variotii	25	-	-	-	Nyilasi et al. (2010)
	Rhizopus oryzae	2–3.125	-	KET, ITR	-	Nyilasi et al. (2010)
	A. fumigatus	2	-	-	-	Nyilasi et al. (2010)
	A. flavus	128	-	KET, MIA, ITR	-	Nyilasi et al. (2010)
Rosuvastatin	*C. albicans*	8–128	-	MIA	-	Nyilasi et al. (2010); Lima et al. (2019)
	C. glabrata	32–128	-	-	-	Nyilasi et al. (2010; Lima et al. (2019)
	C. utilis	200	-	MIA	-	Cabral et al. (2013)
	Paecilomyces variotii	32	-	-	-	Nyilasi et al. (2010)
	Saccharomyces cerevisiae	40	-	CTZ, ITR, MIA	-	Cabral et al. (2013)
	Rhizopus oryzae	> 128	-	KET, ITR	-	Nyilasi et al. (2010)
	A. fumigatus	128	-	ITR	-	Nyilasi et al. (2010)
	A. flavus	> 128	-	-	-	Nyilasi et al. (2010)
Pitavastatin	*C. albicans, C. glabrata, C. auris*	8	*Caenorhabditis elegans*	ITR, VRC, FLC	-	Eldesouky et al. (2020)

Note: *VRC*, voriconazole; *AmB*, amphotericin B; *FLC*, fluconazole; *ITR*, itraconazole; *CTZ*, clotrimazole; *ANI*, anidulafungin; *MIA*, micafungin; -, no relevant studies were mentioned in the corresponding references

highly synergistic effects on *C. albicans* biofilms both *in vitro* and in rat venous catheter biofilm models (Uppuluri et al. 2008). Glucocorticoids, such as hydrocortisone, budesonide, and dexamethasone, are immunosuppressants with antifungal activity (Ramondenc et al. 1998; Li et al. 2016; Sun et al. 2017). However, the antifungal activity of glucocorticoids remains controversial. For instance, an investigation found that hydrocortisone enhanced the growth of *Aspergillus* spp. (Ng et al. 1994). Betamethasone, one of the glucocorticoids, is also capable of promoting hyphal formation, stimulating extracellular phospholipase production, and decreasing the anti–*C. albicans* activity of amphotericin B and nystatin (Jakab et al. 2015). Moreover, an in vivo investigation also found that glucocorticoids increased fungal burden in the gastrointestinal tract in rats (Myerowitz 1981) and enhanced the frequency of fungal translocation in mice (Maraki et al. 1999). Thus, the practical application of glucocorticoids in fungal infections requires further investigation.

Immunosuppressant-treated fungal cells show phenotypes consistent with inhibition of planktonic cell growth, morphological transformation, and biofilm formation (Uppuluri et al. 2008; Jia et al. 2016). However, at present, the exact mechanisms of immunosuppressant synergism with various antifungal drugs have not been delineated. In particular, the TOR as a representative target may be a promising antifungal approach. To date, there are no relevant fungal-specific inhibitors available (Cordeiro et al. 2014). On the other hand, the use of immunosuppressants can inhibit the host immune response, which increases the risk of fungal infection. According to a large number of in vitro antifungal experiments, immunosuppressants do have potent antifungal effects. However, there are no clinical studies to demonstrate whether immunosuppressants have antifungal effects in humans.

Statins

Statins are firstly known as lipid-lowering and cholesterol-lowering drugs as they inhibit HMG-CoA reductase (an essential enzyme in cholesterol biosynthesis) (Esfahani et al. 2019) and are classified according to their hydrophobicity into hydrophilic statins (pravastatin and rosuvastatin) and lipophilic statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin). It has been confirmed that statins exert a broad spectrum of anti-fungal effects on *Candida* spp., *Aspergillus* spp., and Zygomycetes (Callegari et al. 2010). Table 3 shows a brief summary of the statins with antifungal ability. The antifungal mechanism of statins is focused primarily on the biofilm. For example, the changes in the main components of the biofilm or genes associated with fungal biofilm formation following monotherapy or/and synergism of antifungal agents have been verified. Inexplicably, antifungal activity findings are inconsistent. For instance, pravastatin has synergistic effects with fluconazole by inhibiting farnesol production against *C. albicans* (Tashiro et al. 2012), and in contrast, no synergy was found between pravastatin and fluconazole in vitro in another investigation (Nash et al. 2002). In addition, a study even reported that pravastatin did not inhibit the growth of *Candida* spp. (Brilhante et al. 2015). The reason for this may be due to differences in fungi strains and different methodology. These contradictory findings require clarification in further investigations.

Antiarrhythmic drugs

Antiarrhythmic drugs, which are used in the prevention and treatment of tachycardia, bradycardia, or arrhythmia, include sodium channel antagonists, β-receptor blockers, potassium channel blockers (PCRs), and calcium channel blockers (CCBs). Trials have shown that amiodarone, PCRs, and CCBs exhibit favorable antifungal activity when administered alone or combined with conventional antifungals. CCBs, as the name suggests, prevent calcium ions from entering cells and maintain metabolic processes. Verapamil (verapamil hydrochloride), a phenylalkylamine CCB, mainly combats *C. albicans* by affecting hyphal development, adhesion, gastrointestinal colonization, or increasing strain susceptibility to oxidative stress (Yu et al. 2014a, 2014b). In addition, verapamil enhances the antifungal activity of tunicamycin or fluconazole against *C. albicans* during biofilm formation and preformed biofilms (Yu et al. 2013). In *A. fumigatus*, the drug efflux pump was blocked and ergosterol content was decreased following treatment with verapamil and itraconazole simultaneously (Zeng et al. 2019). Other CCBs, such as diltiazem, nicardipine, and nifedipine, have shown antifungal activity against *C. albicans*, *C. glabrata*, Ascomycetous, and Mucoralean fungi, either alone or in combination with antifungals (Bulatova and Darwish 2008; Homa et al. 2017; Alnajjar et al. 2018). Amiodarone is known to block potassium, sodium, and calcium channels and is commonly used to treat and prevent tachyarrhythmia (Kodama et al. 1999; Nattel and Singh 1999; Dorian 2000). In pathogens, amiodarone mainly disrupted calcium homeostasis to elicit high levels of cytoplasmic calcium, leading to cell death in *Cryptococcus* spp., *Aspergillus* spp., *Fusarium oxysporum*, *C. albicans*, *C. tropicalis*, and *Saccharomyces cerevisiae* (Courchesne 2002; Afeltra et al. 2004; Courchesne et al. 2009; Knorre et al. 2009; Gamarra et al. 2010; Bagar and Benčina 2012; Silva et al. 2013). In addition, amiodarone displayed potent fungicidal effects at a low dose combined with fluconazole and miconazole (Gupta et al. 2003). Hence, calcium channels may be potential targets in the therapy of fungal-related infections.

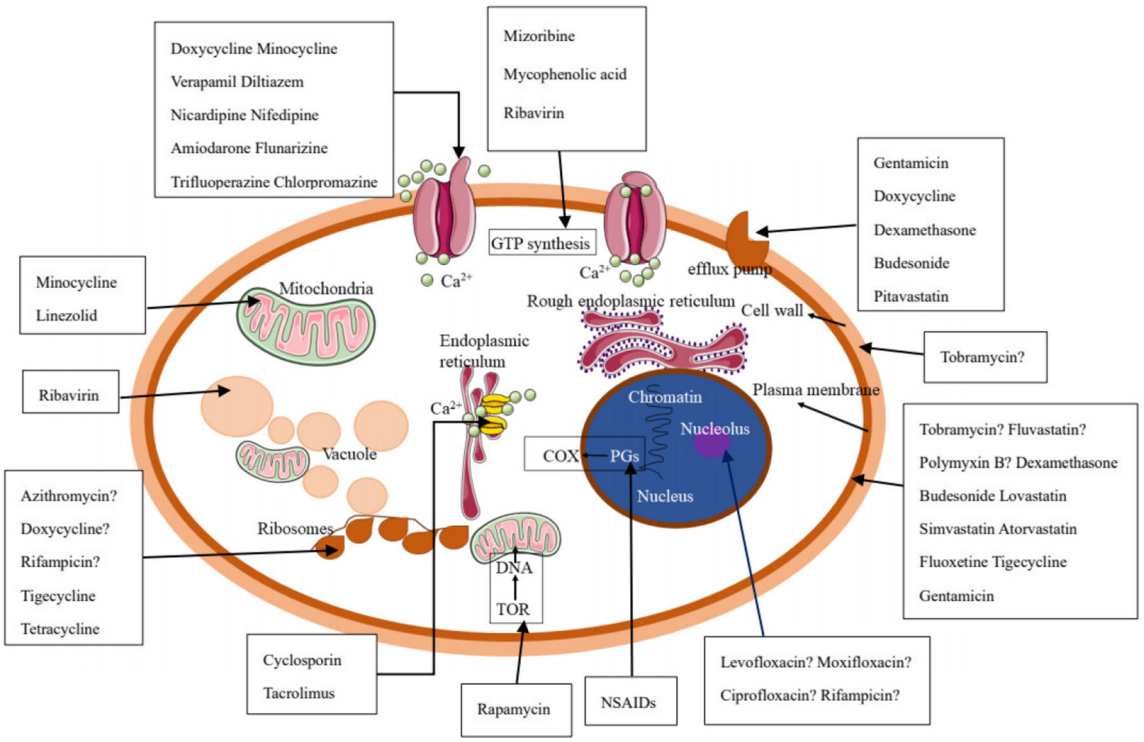

Fig. 1 The antifungal targets of the above-mentioned non-antifungal agents. "?", the target is not clear; COX, cyclooxygenase; PGs, prostaglandins; NSAIDs, non-steroidal anti-inflammatory drugs

Antipsychotic drugs

Antipsychotic drugs include benzamides, butyrophenones, dibenzoxazepine, phenothiazines, and thioxanthene. Phenothiazines are the first generation of antipsychotics and are mainly used to treat schizophrenia and mania. In addition, phenothiazines possess multiple effects such as altering the metabolism of cyclic nucleotides, modifying the structure of membranes, binding to calmodulin and they participate in many intracellular responses (Kim et al. 2019), which may explain the antifungal action of phenothiazines (Wood and Nugent 1985. 1985; Rossato et al. 2016). Chlorpromazine and trifluoperazine are representative phenothiazines. Both block the central dopamine D_2 receptor to improve symptoms in mentally ill patients. They have excellent activity against *Candida* spp. and *C. neoformans* either alone or in combination with ketoconazole and amphotericin B (Wood and Nugent 1985; Ben-Gigi et al. 1988; Sharma et al. 2001; Galgóczy et al. 2011; Rossato et al. 2016). Trifluoperazine also has fungicidal effects on *C. neoformans*, especially on melanized cells (Wang and Casadevall 1996). In addition, chlorpromazine and trifluoperazine have fungicidal effects on Zygomycetes when concentrations reach 25–200 μg/mL. Moreover, it has synergistic effects with amphotericin B (Galgóczy et al. 2009). The minimum fungicidal concentration of chlorpromazine and trifluoperazine in *Aspergillus* spp., *Scedosporium*, and *Pseudallescheria* ranged between 10 and 64 μg/mL (Vitale et al. 2007; Homa et al. 2015). Flunarizine is a difluorinated derivative of piperazine as well as a potent CCB. It has the same structure as phenothiazines. Flunarizine also exhibits broad-spectrum antifungal effects against *Candida* spp., *Cryptococcus* spp., and *Zygosaccharomyces* spp. alone or jointly with ketoconazole in vitro probably by inhibiting calmodulin activity and increasing the penetration of ketoconazole through cell walls (Krajewska-Kułak and Niczyporuk 1993).

Compared to the traditional antifungal drugs, the main advantage of phenothiazines is that they can cross the blood-brain barrier and improve bioavailability. Moreover, the levels achievable in the brain with antipsychotic therapeutic doses range from 50 to 100 μg/mL; however, the range in plasma is only between 0.5 and 1 μg/mL (Homa et al. 2015).

Antidepressant drugs

There are currently many types of antidepressant drugs used in clinics. These mainly include monoamine oxidase inhibitors (e.g., phenelzine), tricyclic (e.g., amitriptyline and doxepin), tetracyclic (e.g., maprotiline), and selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine and paroxetine). Of these, SSRIs are first-line antidepressant drugs with low side effects. They not only have anti-depression activity but also have anti-anxiety activity (Latendresse et al. 2017). SSRIs effectively inhibit the uptake of serotonin by neurons from synaptic spaces. This increases the availability of this neurotransmitter

in these spaces and improves emotional states. As such, SSRIs can be used to treat depressive mental disorders (Bandelow et al. 2017). Encouragingly, SSRIs have been shown to have positive antifungal activity in various studies. An antifungal experiment showed that fluoxetine could kill some azole-resistant *Candida* sp. strains in vitro with or without fluconazole. Moreover, they also improved the survival rate of *Galleria mellonella*. The antifungal mechanism involves inhibition of extracellular phospholipase activity by down-regulated *SAP1-4* genes in resistant *C. albicans* (Oliveira et al. 2014; Gu et al. 2016). The *SAP* genes encode secreted aspartyl proteinases (*SAP*), which are key virulence factors and play an important role in the growth, development, and pathogenicity of *Candida* spp. (Naglik et al. 2003). In addition, fluoxetine exhibited synergistic effects against *C. albicans* biofilms and relieved oral candidiasis in infected mice when combined with caspofungin (Jiang et al. 2020). Sertraline, another type of SSRI, also showed positive antifungal activity alone or in combination with antifungal agents. It can reduce the fungal burden, improve survival rate, and impair tissue damage in mice and *G. mellonella* (Treviño-Rangel Rde et al. 2016; Treviño-Rangel et al. 2019). Similar results showed that sertraline had fungistatic or fungicidal effects in *Candida* spp., *Coccidioides immitis*, *C. neoformans*, *Trichosporon asahii*, and *A. fumigatus* (Cong et al. 2016; Paul et al. 2016; Treviño-Rangel Rde et al. 2016; Oliveira et al. 2018; Treviño-Rangel et al. 2019; Gowri et al. 2020).

Non-steroidal anti-inflammatory drugs

NSAIDs act mainly by inhibiting the activity of cyclooxygenase to reduce the production of prostaglandins (PGs) and thus have antipyretic, analgesic, anti-inflammatory, and other functions (Fitzpatrick 2004). NSAIDs, especially aspirin, etodolac, diclofenac, celecoxib, nimesulide, ibuprofen, meloxicam, ketoprofen, tenoxicam, and ketorolac exhibited favorable anti–*C. albicans* effects by inhibiting the synthesis of fungal PGs, which play an important role in biofilm development, adhesion, and morphogenesis in *C. albicans* (Alem and Douglas 2004; Abdelmegeed and Shaaban 2013). In addition, most of these drugs had synergistic or additive (ketorolac) activity with fluconazole against *C. albicans* (Abdelmegeed and Shaaban 2013). Subsequently, the antifungal mechanisms of aspirin and ibuprofen have become clearer. They can, by activating the high-osmolarity glycerol pathway, induce the accumulation of reactive oxygen species (ROS) and then simultaneously damage the integrity of cell membranes leading to the death of *Cryptococcus* cells (Ogundeji et al. 2016). In addition, aspirin and ibuprofen combined with fluconazole, caspofungin, and amphotericin B have effects on fungi (Ogundeji et al. 2016; Yang et al. 2016). Ibuprofen also has anti-*Sporothrix* activity singly (median MIC of 256 μg/mL) or in combination with antifungal agents including amphotericin B, itraconazole, and terbinafine (Borba-Santos et al. 2021). Diclofenac sodium can downregulate the expression of *Ef-1* gene, which is involved in cellular RNA transport, cell cycle, and apoptosis (Alves et al. 2015), thus resulting in a reduction in the formation of *A. fumigatus* filaments (Nargesi and Rezaie 2018).

Conclusion

In this review, we summarized the antifungal effects of a number of non-antifungal agents. In addition, some antitumor agents such as miltefosine (Wu et al. 2020), tamoxifen (Hai et al. 2019), methotrexate (Yang et al. 2019), and antiepileptic drugs (Kathwate et al. 2015) have been reported to have antifungal effects. The use of drug repurposing strategies in the discovery of novel antifungal agents is a revelation in the identification of new antifungal drugs through structural readjustment. With regard to their related antifungal targets, there are still many antifungal mechanisms of the above-mentioned drugs which are unclear (Fig. 1). To reveal the precise targets, further investigations should be performed using transcriptome analysis and molecular techniques, which will lay the foundation for the development of novel antifungal drugs for example using target design. In addition, these antifungal experiments have only focused on either in vitro studies or animal model experiments. There is not enough clinical evidence to prove their practical use in the clinic. Moreover, many factors, such as changes in medium composition will perhaps lead to different or completely opposite results. In in vivo studies, differences between animal models or homogeneous animal models and differences in pharmacokinetic and pharmacodynamic parameters of compounds in these models, and the effects of host-derived serum and, cellular factors should be clarified. Hence, it is essential to use systematic and standard research approaches and to collect more clinical data to evaluate the antifungal effectiveness of these agents.

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Declarations

Ethics statement This article does not contain any studies on human participants or animals performed by any of the authors.

Conflict of interest The authors declare no competing interests.

References

Abdelmegeed E, Shaaban MI (2013) Cyclooxygenase inhibitors reduce biofilm formation and yeast-hypha conversion of fluconazole resistant *Candida albicans*. J Microbiol 51(5):598–604. https://doi.org/10.1007/s12275-013-3052-6

Afeltra J, Vitale RG, Mouton JW, Verweij PE (2004) Potent synergistic *in vitro* interaction between nonantimicrobial membrane-active compounds and itraconazole against clinical isolates of *Aspergillus fumigatus* resistant to itraconazole. Antimicrob Agents Chemother 48(4):1335–1343. https://doi.org/10.1128/aac.48.4.1335-1343.2004

Aguiar Cordeiro R, de Jesus Evangelista AJ, Serpa R, Colares de Andrade AR, Leite Mendes PB, Silva Franco JD, de Oliveira JS, de Alencar LP, Sales JA, Carneiro Câmara LM, Souza Collares Maia Castelo-Branco D, Nogueira Brilhante RS, Costa Sidrim JJ, Gadelha Rocha MF (2018) β-lactam antibiotics & vancomycin increase the growth & virulence of *Candida* spp. Future Microbiol 13:869–875. https://doi.org/10.2217/fmb-2018-0019

Ajdidi A, Sheehan G, Abu Elteen K, Kavanagh K (2019) Assessment of the *in vitro* and *in vivo* activity of atorvastatin against *Candida albicans*. J Med Microbiol 68(10):1497–1506. https://doi.org/10.1099/jmm.0.001065

Ajdidi A, Sheehan G, Kavanagh K (2020) Exposure of *Aspergillus fumigatus* to atorvastatin leads to altered membrane permeability and induction of an oxidative stress response. J Fungi (Basel) 6(2):42. https://doi.org/10.3390/jof6020042

Alem MA, Douglas LJ (2004) Effects of aspirin and other nonsteroidal anti-inflammatory drugs on biofilms and planktonic cells of *Candida albicans*. Antimicrob Agents Chemother 48(1):41–47. https://doi.org/10.1128/aac.48.1.41-47.2004

Alnajjar LM, Bulatova NR, Darwish RM (2018) Evaluation of four calcium channel blockers as fluconazole resistance inhibitors in *Candida glabrata*. J Glob Antimicrob Resist 14:185–189. https://doi.org/10.1016/j.jgar.2018.04.004

Alves LR, Oliveira C, Goldenberg S (2015) Eukaryotic translation elongation factor-1 alpha is associated with a specific subset of mRNAs in *Trypanosoma cruzi*. BMC Microbiol 15:104. https://doi.org/10.1186/s12866-015-0436-2

Anderson TM, Clay MC, Cioffi AG, Diaz KA, Hisao GS, Tuttle MD, Nieuwkoop AJ, Comellas G, Maryum N, Wang S, Uno BE, Wildeman EL, Gonen T, Rienstra CM, Burke MD (2014) Amphotericin forms an extramembranous and fungicidal sterol sponge. Nat Chem Biol 10(5):400–406. https://doi.org/10.1038/nchembio.1496

Arendrup MC, Cuenca-Estrella M, Lass-Flo¨rl C, Hope WW (2012) EUCAST technical note on *Aspergillus* and amphotericin B, itraconazole, and posaconazole. Clin Microbiol Infect 18(7):E248–E250. https://doi.org/10.1111/j.1469-0691.2012.03890.x

Arrieta O, Barrón F, Padilla MS, Avilés-Salas A, Ramírez-Tirado LA, Arguelles Jiménez MJ, Vergara E, Zatarain-Barrón ZL, Hernández-Pedro N, Cardona AF, Cruz-Rico G, Barrios-Bernal P, Yamamoto Ramos M, Rosell R (2019) Effect of metformin plus tyrosine kinase inhibitors compared with tyrosine kinase inhibitors alone in patients with epidermal growth factor receptor-mutated lung adenocarcinoma: a phase 2 randomized clinical trial. JAMA Oncol 5(11):e192553. https://doi.org/10.1001/jamaoncol.2019.2553

Ashburn TT, Thor KB (2004) Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 3(8):673–683. https://doi.org/10.1038/nrd1468

Baddley JW, Pappas PG (2005) Antifungal combination therapy: clinical potential. Drugs 65(11):1461–1480. https://doi.org/10.2165/00003495-200565110-00002

Bagar T, Benčina M (2012) Antiarrhythmic drug amiodarone displays antifungal activity, induces irregular calcium response and intracellular acidification of *Aspergillus niger* - amiodarone targets calcium and pH homeostasis of *A. niger*. Fungal Genet Biol 49(10):779–791. https://doi.org/10.1016/j.fgb.2012.07.007

Bandelow B, Michaelis S, Wedekind D (2017) Treatment of anxiety disorders. Dialogues Clin Neurosci 19(2):93–107. https://doi.org/10.31887/DCNS.2017.19.2/bbandelow

Bandyopadhyay J, Lee J, Bandyopadhyay A (2004) Regulation of calcineurin, a calcium/calmodulin-dependent protein phosphatase, in *C. elegans*. Mol Cell 18(1):10–16

Banerjee D, Burkard L, Panepinto JC (2014) Inhibition of nucleotide biosynthesis potentiates the antifungal activity of amphotericin B. PLoS One 9(1):e87246. https://doi.org/10.1371/journal.pone.0087246

Bastidas RJ, Shertz CA, Lee SC, Heitman J, Cardenas ME (2012) Rapamycin exerts antifungal activity *in vitro* and *in vivo* against *Mucor circinelloides* via FKBP12-dependent inhibition of Tor. Eukaryot Cell 11(3):270–281. https://doi.org/10.1128/EC.05284-11

Ben-Gigi G, Polacheck I, Eilam Y (1988) *In vitro* synergistic activity of ketoconazole with trifluoperazine and with chlorpromazine against medically important yeasts. Chemotherapy 34(2):96–100. https://doi.org/10.1159/000238554

Bennet JE (1977) Flucytosine. Ann Intern Med 86(3):319–321. https://doi.org/10.7326/0003-4819-86-3-319

Boral H, Metin B, Döğen A, Seyedmousavi S, Ilkit M (2018) Overview of selected virulence attributes in *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton rubrum*, and *Exophiala* dermatitidis. Fungal Genet Biol 111:92–107. https://doi.org/10.1016/j.fgb.2017.10.008

Borba-Santos LP, Nucci M, Ferreira-Pereira A, Rozental S (2021) Anti-*Sporothrix* activity of ibuprofen combined with antifungal. Braz J Microbiol 52(1):101–106. https://doi.org/10.1007/s42770-020-00327-9

Bosetti C, Santucci C, Gallus S, Martinetti M, La Vecchia C (2020) Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. Ann Oncol 31(5):558–568. https://doi.org/10.1016/j.annonc.2020.02.012

Bridges KJ, Li R, Fleseriu M, Cetas JS (2017) *Candida* meningitis after transsphenoidal surgery: a single-institution case series and literature review. World Neurosurg 108:41–49. https://doi.org/10.1016/j.wneu.2017.08.115

Brilhante RS, Caetano EP, Oliveira JS, Castelo-Branco Dde S, Souza ER, Alencar LP, Cordeiro Rde A, Bandeira Tde J, Sidrim JJ, Rocha MF (2015) Simvastatin inhibits planktonic cells and biofilms of *Candida* and *Cryptococcus* species. Braz J Infect Dis 19(5):459–465. https://doi.org/10.1016/j.bjid.2015.06.001

Bulatova NR, Darwish RM (2008) Effect of chemosensitizers on minimum inhibitory concentrations of fluconazole in *Candida albicans*. Med Princ Pract 17(2):117–121. https://doi.org/10.1159/000112964

Burn J, Sheth H, Elliott F, Reed L, Macrae F, Mecklin JP, Möslein G, McRonald FE, Bertario L, Evans DG, Gerdes AM, Ho JWC, Lindblom A, Morrison PJ, Rashbass J, Ramesar R, Seppälä T, Thomas HJW, Pylvänäinen K, Borthwick GM, Mathers JC, Bishop DT, CAPP2 Investigators (2020) Cancer prevention with aspirin in hereditary colorectal cancer (lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet

395(10240):1855–1863. https://doi.org/10.1016/S0140-6736(20)30366-4

Cabral ME, Figueroa LI, Fariña JI (2013) Synergistic antifungal activity of statin-azole associations as witnessed by *Saccharomyces cerevisiae* - and *Candida utilis* - bioassays and ergosterol quantification. Rev Iberoam Micol 30(1):31–38. https://doi.org/10.1016/j.riam.2012.09.006

Callegari S, McKinnon RA, Andrews S, de Barros Lopes MA (2010) Atorvastatin-induced cell toxicity in yeast is linked to disruption of protein isoprenylation. FEMS Yeast Res 10(2):188–198. https://doi.org/10.1111/j.1567-1364.2009.00593.x

Cha Y, Erez T, Reynolds IJ, Kumar D, Ross J, Koytiger G, Kusko R, Zeskind B, Risso S, Kagan E, Papapetropoulos S, Grossman I, Laifenfeld D (2018) Drug repurposing from the perspective of pharmaceutical companies. Br J Pharmacol 175(2):168–180. https://doi.org/10.1111/bph.13798

Chamilos G, Lewis RE, Kontoyiannis DP (2006) Lovastatin has significant activity against zygomycetes and interacts synergistically with voriconazole. Antimicrob Agents Chemother 50(1):96–103. https://doi.org/10.1128/AAC.50.1.96-103.2006

Chang CC, Slavin MA, Chen SCA (2017) New developments and directions in the clinical application of the echinocandins. Arch Toxicol 91(4):1613–1621. https://doi.org/10.1007/s00204-016-1916-3

Chen YL, Yu SJ, Huang HY, Chang YL, Lehman VN, Silao FG, Bigol UG, Bungay AA, Averette A, Heitman J (2014) Calcineurin controls hyphal growth, virulence, and drug tolerance of *Candida tropicalis*. Eukaryot Cell 13(7):844–854. https://doi.org/10.1128/EC.00302-13

Cheung KS, Chan EW, Wong AYS, Chen L, Seto WK, Wong ICK, Leung WK (2019) Metformin use and gastric cancer risk in diabetic patients after helicobacter pylori eradication. J Natl Cancer Inst 111(5):484–489. https://doi.org/10.1093/jnci/djy144

Chin NX, Weitzman I, Della-Latta P (1997) *In vitro* activity of fluvastatin, a cholesterol-lowering agent, and synergy with fluconazole and itraconazole against *Candida* species and *Cryptococcus neoformans*. Antimicrob Agents Chemother 41(4):850–852. https://doi.org/10.1128/AAC.41.4.850

Chowdhary A, Tarai B, Singh A, Sharma A (2020) Multidrug-resistant *Candida auris* infections in critically ill coronavirus disease patients, India, April-July 2020. Emerg Infect Dis 26(11):2694–2696. https://doi.org/10.3201/eid2611.203504

Chuck SL, Sande MA (1989) Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. N Engl J Med 321(12):794–799. https://doi.org/10.1056/NEJM198909213211205

Cong L, Liao Y, Yang S, Yang R (2016) *In vitro* antifungal activity of sertraline and synergistic effects in combination with antifungal drugs against planktonic forms and biofilms of clinical *Trichosporon asahii* isolates. PLoS One 11(12):e0167903. https://doi.org/10.1371/journal.pone.0167903

Cordeiro RA, Macedo RB, Teixeira CEC, Marques FJF, Bandeira TJPG, Moreira JLB, Brilhante RSN, Rocha MFG, Sidrim JJC (2014) The calcineurin inhibitor cyclosporin A exhibits synergism with antifungals against *Candida parapsilosis* species complex. J Med Microbiol 63(Pt 7):936–944. https://doi.org/10.1099/jmm.0.073478-0

Courchesne WE (2002) Characterization of a novel, broad-based fungicidal activity for the antiarrhythmic drug amiodarone. J Pharmacol Exp Ther 300(1):195–199. https://doi.org/10.1124/jpet.300.1.195

Courchesne WE, Tunc M, Liao S (2009) Amiodarone induces stress responses and calcium flux mediated by the cell wall in *Saccharomyces cerevisiae*. Can J Microbiol 55(3):288–303. https://doi.org/10.1139/w08-132

Cruz MC, Goldstein AL, Blankenship J, Del Poeta M, Perfect JR, McCusker JH, Bennani YL, Cardenas ME, Heitman J (2001) Rapamycin and less immunosuppressive analogs are toxic to *Candida albicans* and *Cryptococcus neoformans* via FKBP12-dependent inhibition of TOR. Antimicrob Agents Chemother 45(11):3162–3170. https://doi.org/10.1128/AAC.45.11.3162-3170.2001

Cuny GD, Suebsuwong C, Ray SS (2017) Inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitors: a patent and scientific literature review (2002-2016). Expert Opin Ther Pat 27(6):677–690. https://doi.org/10.1080/13543776.2017.1280463

Deaguero IG, Huda MN, Rodriguez V, Zicari J, Al-Hilal TA, Badruddoza AZM, Nurunnabi M (2020) Nano-vesicle based antifungal formulation shows higher stability, skin diffusion, biosafety and anti-fungal efficacy *in vitro*. Pharmaceutics 12(6):516. https://doi.org/10.3390/pharmaceutics12060516

Del Pozo JL, Francés ML, Hernáez S, Serrera A, Alonso M, Rubio MF (2011) Effect of amphotericin B alone or in combination with rifampicin or clarithromycin against *Candida* species biofilms. Int J Artif Organs 34(9):766–770. https://doi.org/10.5301/ijao.5000023

Denning DW (2003) Echinocandin antifungal drugs. Lancet 362(9390):1142–1151. https://doi.org/10.1016/S0140-6736(03)14472-8

Deren YT, Ozdek S, Kalkanci A, Akyürek N, Hasanreisoğlu B (2010) Comparison of antifungal efficacies of moxifloxacin, liposomal amphotericin B, and combination treatment in experimental *Candida albicans* endophthalmitis in rabbits. Can J Microbiol 56(1):1–7. https://doi.org/10.1139/w09-112

Dorian P (2000) Mechanisms of action of class III agents and their clinical relevance. Europace 1(Suppl C):C6–C9

Drgona L, Khachatryan A, Stephens J, Charbonneau C, Kantecki M, Haider S, Barnes R (2014) Clinical and economic burden of invasive fungal diseases in Europe: focus on pre-emptive and empirical treatment of *Aspergillus* and *Candida* species. Eur J Clin Microbiol Infect Dis 33(1):7–21. https://doi.org/10.1007/s10096-013-1944-3

Du H, Bing J, Hu T, Ennis CL, Nobile CJ, Huang G (2020) *Candida auris*: epidemiology, biology, antifungal resistance, and virulence. PLoS Pathog 16(10):e1008921. https://doi.org/10.1371/journal.ppat.1008921

Dy ABC, Tassone F, Eldeeb M, Salcedo-Arellano MJ, Tartaglia N, Hagerman R (2018) Metformin as targeted treatment in fragile X syndrome. Clin Genet 93(2):216–222. https://doi.org/10.1111/cge.13039

El-Azizi M (2007) Enhancement of the *in vitro* activity of amphotericin B against the biofilms of non-*albicans Candida* spp. by rifampicin and doxycycline. J Med Microbiol 56(Pt 5):645–649. https://doi.org/10.1099/jmm.0.46952-0

Eldesouky HE, Salama EA, Li X, Hazbun TR, Mayhoub AS, Seleem MN (2020) Repurposing approach identifies pitavastatin as a potent azole chemosensitizing agent effective against azole-resistant *Candida* species. Sci Rep 10(1):7525. https://doi.org/10.1038/s41598-020-64571-7

Ellis D (2002) Amphotericin B: spectrum and resistance. J Antimicrob Chemother 49(Suppl 1):7–10. https://doi.org/10.1093/jac/49.suppl_1.7

Emami S, Tavangar P, Keighobadi M (2017) An overview of azoles targeting sterol 14α-demethylase for antileishmanial therapy. Eur J Med Chem 135:241–259. https://doi.org/10.1016/j.ejmech.2017.04.044

Emri T, Majoros L, Tóth V, Pócsi I (2013) Echinocandins: production and applications. Appl Microbiol Biotechnol 97(8):3267–3284. https://doi.org/10.1007/s00253-013-4761-9

Esfahani AN, Golestannejad Z, Khozeimeh F, Dehghan P, Maheronnaghsh M, Zarei Z (2019) Antifungal effect of atorvastatin against *Candida* species in comparison to fluconazole and nystatin. Med Pharm Rep 92(4):368–373. https://doi.org/10.15386/mpr-1209

Fernández-Rivero ME, Del Pozo JL, Valentín A, de Diego AM, Pemán J, Cantón E (2017) Activity of amphotericin B and anidulafungin combined with rifampicin, clarithromycin, ethylenediaminetetraacetic acid, N-acetylcysteine, and farnesol against *Candida tropicalis*

biofilms. J Fungi (Basel) 3(1):16. https://doi.org/10.3390/jof3010016

Fiori A, Van Dijck P (2012) Potent synergistic effect of doxycycline with fluconazole against *Candida albicans* is mediated by interference with iron homeostasis. Antimicrob Agents Chemother 56(7):3785–3796. https://doi.org/10.1128/AAC.06017-11

Fitzpatrick FA (2004) Cyclooxygenase enzymes: regulation and function. Curr Pharm Des 10(6):577–588. https://doi.org/10.2174/1381612043453144

Galgóczy L, Papp T, Kovács L, Ordögh L, Vágvölgyi C (2009) *In vitro* activity of phenothiazines and their combinations with amphotericin B against Zygomycetes causing rhinocerebral zygomycosis. Med Mycol 47(3):331–335. https://doi.org/10.1080/13693780802378853

Galgóczy L, Bácsi A, Homa M, Virágh M, Papp T, Vágvölgyi C (2011) *In vitro* antifungal activity of phenothiazines and their combination with amphotericin B against different *Candida* species. Mycoses 54(6):e737–e743. https://doi.org/10.1111/j.1439-0507.2010.02010.x

Gamarra S, Rocha EM, Zhang YQ, Park S, Rao R, Perlin DS (2010) Mechanism of the synergistic effect of amiodarone and fluconazole in *Candida albicans*. Antimicrob Agents Chemother 54(5):1753–1761. https://doi.org/10.1128/AAC.01728-09

Gao Y, Zhang C, Lu C, Liu P, Li Y, Li H, Sun S (2013) Synergistic effect of doxycycline and fluconazole against *Candida albicans* biofilms and the impact of calcium channel blockers. FEMS Yeast Res 13(5):453–462. https://doi.org/10.1111/1567-1364.12048

Gao Y, Li H, Liu S, Zhang X, Sun S (2014) Synergistic effect of fluconazole and doxycycline against *Candida albicans* biofilms resulting from calcium fluctuation and downregulation of fluconazole - inducible efflux pump gene overexpression. J Med Microbiol 63(Pt 7):956–961. https://doi.org/10.1099/jmm.0.072421-0

Gao L, Sun Y, Yuan M, Li M, Zeng T (2020) *In vitro* and *in vivo* study on the synergistic effect of minocycline and azoles against pathogenic fungi. Antimicrob Agents Chemother 64(6):e00290–e00220. https://doi.org/10.1128/AAC.00290-20

Garbino J (2004) Caspofungin–a new therapeutic option for oropharyngeal candidiasis. Clin Microbiol Infect 10(3):187–189. https://doi.org/10.1111/j.1198-743x.2004.00823.x

Gil-Alonso S, Jauregizar N, Eraso E, Quindós G (2015) Postantifungal effect of micafungin against the species complexes of *Candida albicans* and *Candida parapsilosis*. PLoS One 10(7):e0132730. https://doi.org/10.1371/journal.pone.0132730

Gowri M, Sofi Beaula W, Biswal J, Dhamodharan P, Saiharish R, Rohan prasad S, Pitani R, Kandaswamy D, Raghunathan R, Jeyakanthan J, Rayala SK, Venkatraman G (2016) β-lactam substituted polycyclic fused pyrrolidine/pyrrolizidine derivatives eradicate *C. albicans* in an *ex vivo* human dentinal tubule model by inhibiting sterol 14-α demethylase and cAMP pathway. Biochim Biophys Acta 1860(4):636–647. https://doi.org/10.1016/j.bbagen.2015.12.020

Gowri M, Jayashree B, Jeyakanthan J, Girija EK (2020) Sertraline as a promising antifungal agent: inhibition of growth and biofilm of *Candida auris* with special focus on the mechanism of action *in vitro*. J Appl Microbiol 128(2):426–437. https://doi.org/10.1111/jam.14490

Greene RA, Adams KK, Rogers RD, Berard-Collins C, Lorenzo MP (2020) Pharmacokinetics of flucytosine in a critically ill patient on continuous venovenous hemodiafiltration. Am J Health Syst Pharm 77(8):609–613. https://doi.org/10.1093/ajhp/zxaa034

Gu W, Guo D, Zhang L, Xu D, Sun S (2016) The synergistic effect of azoles and fluoxetine against resistant *Candida albicans* strains is attributed to attenuating fungal virulence. Antimicrob Agents Chemother 60(10):6179–6188. https://doi.org/10.1128/AAC.03046-15

Gu W, Yu Q, Yu C, Sun S (2018) *In vivo* activity of fluconazole/tetracycline combinations in *Galleria mellonella* with resistant *Candida albicans* infection. J Glob Antimicrob Resist 13:74–80. https://doi.org/10.1016/j.jgar.2017.11.011

Gupta SS, Ton VK, Beaudry V, Rulli S, Cunningham K, Rao R (2003) Antifungal activity of amiodarone is mediated by disruption of calcium homeostasis. J Biol Chem 278(31):28831–28839. https://doi.org/10.1074/jbc.M303300200

Hai TP, Van AD, Ngan NTT, Nhat LTH, Lan NPH, Vinh Chau NV, Thwaites GE, Krysan D, Day JN (2019) The combination of tamoxifen with amphotericin B, but not with fluconazole, has synergistic activity against the majority of clinical isolates of *Cryptococcus neoformans*. Mycoses 62(9):818–825. https://doi.org/10.1111/myc.12955

Haidar G, Singh N (2018) How we approach combination antifungal therapy for invasive aspergillosis and mucormycosis in transplant recipients. Transplantation 102(11):1815–1823. https://doi.org/10.1097/TP.0000000000002353

High KP, Washburn RG (1997) Invasive aspergillosis in mice immunosuppressed with cyclosporin A, tacrolimus (FK506), or sirolimus (rapamycin). J Infect Dis 175(1):222–225. https://doi.org/10.1093/infdis/175.1.222

Homa M, Galgóczy L, Tóth E, Tóth L, Papp T, Chandrasekaran M, Kadaikunnan S, Alharbi NS, Vágvölgyi C (2015) *In vitro* antifungal activity of antipsychotic drugs and their combinations with conventional antifungals against *Scedosporium* and *Pseudallescheria* isolates. Med Mycol 53(8):890–895. https://doi.org/10.1093/mmy/myv064

Homa M, Hegedűs K, Fülöp Á, Wolfárt V, Kadaikunnan S, Khaled JM, Alharbi NS, Vágvölgyi C, Galgóczy L (2017) *In vitro* activity of calcium channel blockers in combination with conventional antifungal agents against clinically important filamentous fungi. Acta Biol Hung 68(3):334–344. https://doi.org/10.1556/018.68.2017.3.10

Jakab Á, Emri T, Sipos L, Kiss Á, Kovács R, Dombrádi V, Kemény-Beke Á, Balla J, Majoros L, Pócsi I (2015) Betamethasone augments the antifungal effect of menadione–towards a novel anti-*Candida albicans* combination therapy. J Basic Microbiol 55(8):973–981. https://doi.org/10.1002/jobm.201400903

Jia W, Zhang H, Li C, Li G, Liu X, Wei J (2016) The calcineruin inhibitor cyclosporine a synergistically enhances the susceptibility of *Candida albicans* biofilms to fluconazole by multiple mechanisms. BMC Microbiol 16(1):113. https://doi.org/10.1186/s12866-016-0728-1

Jiang L, Zheng L, Sun KA, Zhou P, Xu R, Gu J, Wei X (2020) *In vitro* and *in vivo* evaluation of the antifungal activity of fluoxetine combined with antifungals against *Candida albicans* biofilms and oral candidiasis. Biofouling 36(5):537–548. https://doi.org/10.1080/08927014.2020.1777401

Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y, THALES investigators (2020) Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. N Engl J Med 383(3):207–217. https://doi.org/10.1056/NEJMc2027491

Kathwate GH, Shinde RB, Karuppayil SM (2015) Antiepileptic drugs inhibit growth, dimorphism, and biofilm mode of growth in human pathogen *Candida albicans*. Assay Drug Dev Technol 13(6):307–312. https://doi.org/10.1089/adt.2015.29007.ghkdrrr

Keçeli SA, Willke A, Tamer GS, Boral OB, Sonmez N, Cağatay P (2014) Interaction between caspofungin or voriconazole and cefoperazone-sulbactam or piperacillin-tazobactam by *in vitro* and *in vivo* methods. APMIS 122(5):412–417. https://doi.org/10.1111/apm.12159

Kim JH, Chan KL, Cheng LW, Tell LA, Byrne BA, Clothier K, Land KM (2019) High efficiency drug repurposing design for new antifungal agents. Methods Protoc 2(2):31. https://doi.org/10.3390/mps2020031

Knorre DA, Krivonosova TN, Markova OV, Severin FF (2009) Amiodarone inhibits multiple drug resistance in yeast

Saccharomyces cerevisiae. Arch Microbiol 191(8):675–679. https://doi.org/10.1007/s00203-009-0493-8

Kodama I, Kamiya K, Toyama J (1999) Amiodarone: ionic and cellular mechanisms of action of the most promising class III agent. Am J Cardiol 84(9A):20R–28R. https://doi.org/10.1016/s0002-9149(99)00698-0

Köhler GA, Gong X, Bentink S, Theiss S, Pagani GM, Agabian N, Hedstrom L (2005) The functional basis of mycophenolic acid resistance in *Candida albicans* IMP dehydrogenase. J Biol Chem 280(12):11295–11302. https://doi.org/10.1074/jbc.M409847200

Kontoyiannis DP, Lewis RE, Osherov N, Albert ND, May GS (2003) Combination of caspofungin with inhibitors of the calcineurin pathway attenuates growth *in vitro* in *Aspergillus* species. J Antimicrob Chemother 51(2):313–316. https://doi.org/10.1093/jac/dkg090

Kouvari M, Panagiotakos DB, Chrysohoou C, Yannakoulia M, Georgousopoulou EN, Tousoulis D, Pitsavos C, ATTICA study investigators (2020) Dietary vitamin D intake, cardiovascular disease and cardiometabolic risk factors: a sex-based analysis from the ATTICA cohort study. J Hum Nutr Diet 33(5):708–717. https://doi.org/10.1111/jhn.12748

Krajewska-Kułak E, Niczyporuk WW (1993) Anticandidal activity of flunarizine. Mater Med Pol 25(3-4):143–144

Ku TS, Palanisamy SK, Lee SA (2010) Susceptibility of *Candida albicans* biofilms to azithromycin, tigecycline and vancomycin and the interaction between tigecycline and antifungals. Int J Antimicrob Agents 36(5):441–446. https://doi.org/10.1016/j.ijantimicag.2010.06.034

Kubiça TF, Denardi LB, Azevedo MI, Oliveira V, Severo LC, Santurio JM, Alves SH (2016) Antifungal activities of tacrolimus in combination with antifungal agents against fluconazole-susceptible and fluconazole-resistant *Trichosporon asahii* isolates. Braz J Infect Dis 20(6):539–545. https://doi.org/10.1016/j.bjid.2016.08.008

Kummari LK, Butler MS, Furlong E, Blundell R, Nouwens A, Silva AB, Kappler U, Fraser JA, Kobe B, Cooper MA, Robertson AAB (2018) Antifungal benzo[b]thiophene 1,1-dioxide IMPDH inhibitors exhibit pan-assay interference (PAINS) profiles. Bioorg Med Chem 26(20):5408–5419. https://doi.org/10.1016/j.bmc.2018.09.004

Latendresse G, Elmore C, Deneris A (2017) Selective serotonin reuptake inhibitors as first-line antidepressant therapy for perinatal depression. J Midwifery Womens Health 62(3):317–328. https://doi.org/10.1111/jmwh.12607

Lee J, Yesilkanal AE, Wynne JP, Frankenberger C, Liu J, Yan J, Elbaz M, Rabe DC, Rustandy FD, Tiwari P, Grossman EA, Hart PC, Kang C, Sanderson SM, Andrade J, Nomura DK, Bonini MG, Locasale JW, Rosner MR (2019) Effective breast cancer combination therapy targeting BACH1 and mitochondrial metabolism. Nature 568(7751):254–258. https://doi.org/10.1038/s41586-019-1005-x

Lestrade PP, Meis JF, Arends JP, van der Beek MT, de Brauwer E, van Dijk K, de Greeff SC, Haas PJ, Hodiamont CJ, Kuijper EJ, Leenstra T, Muller AE, Oude Lashof AM, Rijnders BJ, Roelofsen E, Rozemeijer W, Tersmette M, Terveer EM, Verduin CM, Wolfhagen MJ, Melchers WJ, Verweij PE (2016) Diagnosis and management of aspergillosis in the Netherlands: a national survey. Mycoses 59(2):101–107. https://doi.org/10.1111/myc.12440

Lestrade PPA, Meis JF, Melchers WJG, Verweij PE (2019) Triazole resistance in *Aspergillus fumigatus*: recent insights and challenges for patient management. Clin Microbiol Infect 25(7):799–806. https://doi.org/10.1016/j.cmi.2018.11.027

Lew MA, Beckett KM, Levin MJ (1977) Antifungal activity of four tetracycline analogues against *Candida albicans in vitro*: potentiation by amphotericin B. J Infect Dis 136(2):263–270. https://doi.org/10.1093/infdis/136.2.263

Li X, Yu C, Huang X, Sun S (2016) Synergistic effects and mechanisms of budesonide in combination with fluconazole against resistant *Candida albicans*. PLoS One 11(12):e0168936. https://doi.org/10.1371/journal.pone.0168936

Lima WG, Alves-Nascimento LA, Andrade JT, Vieira L, de Azambuja Ribeiro RIM, Thomé RG, Dos Santos HB, Ferreira JMS, Soares AC (2019) Are the statins promising antifungal agents against invasive candidiasis? Biomed Pharmacother 111:270–281. https://doi.org/10.1016/j.biopha.2018.12.076

Limon JJ, Skalski JH, Underhill DM (2017) Commensal fungi in health and disease. Cell Host Microbe 22(2):156–165. https://doi.org/10.1016/j.chom.2017.07.002

Liu J, Ran Z, Wang F, Xin C, Xiong B, Song Z (2020) Role of pulmonary microorganisms in the development of chronic obstructive pulmonary disease. Crit Rev Microbiol 47(1):1–12. https://doi.org/10.1080/1040841X.2020.1830748

Loreto ES, Tondolo JS, Pilotto MB, Alves SH, Santurio JM (2014) New insights into the *in vitro* susceptibility of *Pythium insidiosum*. Antimicrob Agents Chemother 58(12):7534–7537. https://doi.org/10.1128/AAC.02680-13

Lu M, Yu C, Cui X, Shi J, Yuan L, Sun S (2018) Gentamicin synergises with azoles against drug-resistant *Candida albicans*. Int J Antimicrob Agents 51(1):107–114. https://doi.org/10.1016/j.ijantimicag.2017.09.012

Lu M, Yang X, Yu C, Gong Y, Yuan L, Hao L, Sun S (2019) Linezolid in combination with azoles induced synergistic effects against *Candida albicans* and protected *Galleria mellonella* against experimental candidiasis. Front Microbiol 9:3142. https://doi.org/10.3389/fmicb.2018.03142

Maraki S, Hajiioannou I, Anatoliotakis N, Plataki M, Chatzinikolaou I, Zoras O, Tselentis Y, Samonis G (1999) Ceftriaxone and dexamethasone affecting yeast gut flora in experimental mice. J Chemother 11(5):363–366. https://doi.org/10.1179/joc.1999.11.5.363

Marchetti O, Entenza JM, Sanglard D, Bille J, Glauser MP, Moreillon P (2000a) Fluconazole plus cyclosporine: a fungicidal combination effective against experimental endocarditis due to *Candida albicans*. Antimicrob Agents Chemother 44(11):2932–2938. https://doi.org/10.1128/aac.44.11.2932-2938.2000

Marchetti O, Moreillon P, Glauser MP, Bille J, Sanglard D (2000b) Potent synergism of the combination of fluconazole and cyclosporine in *Candida albicans*. Antimicrob Agents Chemother 44(9):2373–2381. https://doi.org/10.1128/aac.44.9.2373-2381.2000

Medoff G, Comfort M, Kobayashi GS (1971) Synergistic action of amphotericin B and 5-fluorocytosine against yeast-like organisms. Proc Soc Exp Biol Med 138(2):571–574. https://doi.org/10.3181/00379727-138-35943

Meis JF, Chowdhary A, Rhodes JL, Fisher MC, Verweij PE (2016) Clinical implications of globally emerging azole resistance in *Aspergillus fumigatus*. Philos Trans R Soc Lond Ser B Biol Sci 371(1709):20150460. https://doi.org/10.1098/rstb.2015.0460

Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J (2020) Association of vitamin D status and other clinical characteristics with COVID-19 test results. JAMA Netw Open 3(9):e2019722. https://doi.org/10.1001/jamanetworkopen.2020.19722

Miceli MH, Bernardo SM, Lee SA (2009) *In vitro* analyses of the combination of high-dose doxycycline and antifungal agents against *Candida albicans* biofilms. Int J Antimicrob Agents 34(4):326–332. https://doi.org/10.1016/j.ijantimicag.2009.04.011

Mohamadzadeh M, Zarei M, Vessal M (2020) Synthesis, *in vitro* biological evaluation and in silico molecular docking studies of novel β-lactam-anthraquinone hybrids. Bioorg Chem 95:103515. https://doi.org/10.1016/j.bioorg.2019.103515

Mohan M, Al-Talabany S, McKinnie A, Mordi IR, Singh JSS, Gandy SJ, Baig F, Hussain MS, Bhalraam U, Khan F, Choy AM, Matthew S, Houston JG, Struthers AD, George J, Lang CC (2019) A randomized controlled trial of metformin on left ventricular hypertrophy in patients with coronary artery disease without diabetes: the MET-REMODEL trial. Eur Heart J 40(41):3409–3417. https://doi.org/10.1093/eurheartj/ehz203

Moneib NA (1995) *In-vitro* activity of commonly used antifungal agents in the presence of rifampin, polymyxin B and norfloxacin against *Candida albicans*. J Chemother 7(6):525–529. https://doi.org/10.1179/joc.1995.7.6.525

Montgomerie JZ, Edwards JE Jr, Guze LB (1975) Synergism of amphotericin B and 5-fluorocytosine for *Candida* species. J Infect Dis 132(1):82–86. https://doi.org/10.1093/infdis/132.1.82

Morrow CA, Valkov E, Stamp A, Chow EW, Lee IR, Wronski A, Williams SJ, Hill JM, Djordjevic JT, Kappler U, Kobe B, Fraser JA (2012) *De novo* GTP biosynthesis is critical for virulence of the fungal pathogen *Cryptococcus neoformans*. PLoS Pathog 8(10):e1002957. https://doi.org/10.1371/journal.ppat.1002957

Myerowitz RL (1981) Gastrointestinal and disseminated candidiasis. An experimental model in the immunosuppressed rat. Arch Pathol Lab Med 105(3):138–143

Naglik JR, Challacombe SJ, Hube B (2003) *Candida albicans* secreted aspartyl proteinases in virulence and pathogenesis. Microbiol Mol Biol Rev 67(3):400–428. https://doi.org/10.1128/mmbr.67.3.400-428.2003

Nargesi S, Rezaie S (2018) Investigation an antifungal activity of diclofenac sodium against hyphae formation in *Aspergillus fumigatus* with attention to the expression of *Ef-1* gene. Iran J Public Health 47(5):770–772

Nash JD, Burgess DS, Talbert RL (2002) Effect of fluvastatin and pravastatin, HMG-CoA reductase inhibitors, on fluconazole activity against *Candida albicans*. J Med Microbiol 51(2):105–109. https://doi.org/10.1099/0022-1317-51-2-105

Nattel S, Singh BN (1999) Evolution, mechanisms, and classification of antiarrhythmic drugs: focus on class III actions. Am J Cardiol 84(9A):11R–19R. https://doi.org/10.1016/s0002-9149(99)00697-9

Ng TT, Robson GD, Denning DW (1994) Hydrocortisone-enhanced growth of *Aspergillus* spp.: implications for pathogenesis. Microbiology (Reading) 140(Pt 9):2475–2479. https://doi.org/10.1099/13500872-140-9-2475

Ng K, Nimeiri HS, McCleary NJ, Abrams TA, Yurgelun MB, Cleary JM, Rubinson DA, Schrag D, Miksad R, Bullock AJ, Allen J, Zuckerman D, Chan E, Chan JA, Wolpin BM, Constantine M, Weckstein DJ, Faggen MA, Thomas CA, Kournioti C, Yuan C, Ganser C, Wilkinson B, Mackintosh C, Zheng H, Hollis BW, Meyerhardt JA, Fuchs CS (2019) Effect of high-dose vs standard-dose vitamin D_3 supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: the SUNSHINE randomized clinical trial. JAMA 321(14):1370–1379. https://doi.org/10.1001/jama.2019.2402

Nguyen MH, Clancy CJ, Yu YC, Lewin AS (1997) Potentiation of antifungal activity of amphotericin B by azithromycin against *Aspergillus* species. Eur J Clin Microbiol Infect Dis 16(11):846–848. https://doi.org/10.1007/BF01700417

Nyilasi I, Kocsubé S, Krizsán K, Galgóczy L, Pesti M, Papp T, Vágvölgyi C (2010) *In vitro* synergistic interactions of the effects of various statins and azoles against some clinically important fungi. FEMS Microbiol Lett 307(2):175–184. https://doi.org/10.1111/j.1574-6968.2010.01972.x

O'Driscoll M, Greenhalgh K, Young A, Turos E, Dickey S, Lim DV (2008) Studies on the antifungal properties of N-thiolated beta-lactams. Bioorg Med Chem 16(16):7832–7837. https://doi.org/10.1016/j.bmc.2008.06.035

Ogundeji AO, Pohl CH, Sebolai OM (2016) Repurposing of aspirin and ibuprofen as candidate anti-*Cryptococcus* drugs. Antimicrob Agents Chemother 60(8):4799–4808. https://doi.org/10.1128/AAC.02810-15

Oliveira AS, Gaspar CA, Palmeira-de-Oliveira R, Martinez-de-Oliveira J, Palmeira-de-Oliveira A (2014) Anti-*Candida* activity of fluoxetine alone and combined with fluconazole: a synergistic action against fluconazole -resistant strains. Antimicrob Agents Chemother 58(7):4224–4226. https://doi.org/10.1128/AAC.02623-13

Oliveira AS, Martinez-de-Oliveira J, Donders GGG, Palmeira-de-Oliveira R, Palmeira-de-Oliveira A (2018) Anti-*Candida* activity of antidepressants sertraline and fluoxetine: effect upon pre-formed biofilms. Med Microbiol Immunol 207(3-4):195–200. https://doi.org/10.1007/s00430-018-0539-0

O'Shaughnessy EM, Meletiadis J, Stergiopoulou T, Demchok JP, Walsh TJ (2006) Antifungal interactions within the triple combination of amphotericin B, caspofungin and voriconazole against *Aspergillus* species. J Antimicrob Chemother 58(6):1168–1176. https://doi.org/10.1093/jac/dkl392

Ostrosky-Zeichner L, Marr KA, Rex JH, Cohen SH (2003) Amphotericin B: time for a new "gold standard". Clin Infect Dis 37(3):415–425. https://doi.org/10.1086/376634

Ozcan SK, Budak F, Willke A, Filiz S, Costur P, Dalcik H (2006) Efficacies of caspofungin and a combination of caspofungin and meropenem in the treatment of murine disseminated candidiasis. APMIS 114(12):829–836. https://doi.org/10.1111/j.1600-0463.2006.apm_450.x

Ozdek SC, Miller D, Flynn PM, Flynn HW (2006) *In vitro* antifungal activity of the fourth generation fluoroquinolones against *Candida* isolates from human ocular infections. Ocul Immunol Inflamm 14(6):347–351. https://doi.org/10.1080/09273940600976953

Paassen J, Russcher A, In't Veld-van Wingerden AW, Verweij PE, Kuijper EJ (2016) Emerging aspergillosis by azole-resistant *Aspergillus fumigatus* at an intensive care unit in the Netherlands, 2010 to 2013. Euro Surveill 21(30). https://doi.org/10.2807/1560-7917.ES.2016.21.30.30300

Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE (2016) Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin Infect Dis 63(4):e1–e60. https://doi.org/10.1093/cid/ciw326

Paul S, Mortimer RB, Mitchell M (2016) Sertraline demonstrates fungicidal activity *in vitro* for *Coccidioides immitis*. Mycology 7(3):99–101. https://doi.org/10.1080/21501203.2016.1204368

Pellon A, Ramirez-Garcia A, Buldain I, Antoran A, Martin-Souto L, Rementeria A, Hernando FL (2018) Pathobiology of *Lomentospora prolificans*: could this species serve as a model of primary antifungal resistance? Int J Antimicrob Agents 51(1):10–15. https://doi.org/10.1016/j.ijantimicag.2017.06.009

Perlin DS (2020) Cell wall-modifying antifungal drugs. Curr Top Microbiol Immunol 425:255–275. https://doi.org/10.1007/82_2019_188

Prazynska M, Gospodarek E (2014) *In vitro* effect of amphotericin B on *Candida albicans*, *Candida glabrata* and *Candida parapsilosis* biofilm formation. Mycopathologia 177(1-2):19–27. https://doi.org/10.1007/s11046-014-9727-7

Ramage G, VandeWalle K, Bachmann SP, Wickes BL, López-Ribot JL (2002) *In vitro* pharmacodynamic properties of three antifungal agents against preformed *Candida albicans* biofilms determined by time-kill studies. Antimicrob Agents Chemother 46(11):3634–3636. https://doi.org/10.1128/aac.46.11.3634-3636.2002

Ramondenc I, Pinel C, Ambroise-Thomas P, Grillot R (1998) Does hydrocortisone modify the *in vitro* susceptibility of *Aspergillus fumigatus* to itraconazole and amphotericin B? Med Mycol 36(2):69–73

Ran Z, Liu J, Wang F, Xin C, Shen X, Zeng S, Song Z, Xiong B (2020) Analysis of pulmonary microbial diversity in patients with advanced lung cancer based on high-throughput sequencing technology. Zhongguo Fei Ai Za Zhi 23(12):1031–1038. https://doi.org/10.3779/j.issn.1009-3419.2020.103.16

Ribeiro NQ, Costa MC, Magalhães TFF, Carneiro HCS, Oliveira LV, Fontes ACL, Santos JRA, Ferreira GF, Araujo GRS, Alves V, Frases S, Paixão TA, de Resende Stoianoff MA, Santos DA

(2017) Atorvastatin as a promising anticryptococcal agent. Int J Antimicrob Agents 49(6):695–702. https://doi.org/10.1016/j.ijantimicag.2017.04.005

Robbins N, Wright GD, Cowen LE (2016) Antifungal drugs: the current armamentarium and development of new agents. Microbiol Spectr 4(5). https://doi.org/10.1128/microbiolspec.FUNK-0002-2016

Robbins N, Caplan T, Cowen LE (2017) Molecular evolution of antifungal drug resistance. Annu Rev Microbiol 71:753–775. https://doi.org/10.1146/annurev-micro-030117-020345

Roden MM, Nelson LD, Knudsen TA, Jarosinski PF, Starling JM, Shiflett SE, Calis K, DeChristoforo R, Donowitz GR, Buell D, Walsh TJ (2003) Triad of acute infusion-related reactions associated with liposomal amphotericin B: analysis of clinical and epidemiological characteristics. Clin Infect Dis 36(10):1213–1220. https://doi.org/10.1086/374553

Rossato L, Loreto ÉS, Venturini TP, Azevedo MI, Weiblen C, Botton SA, Santurio JM, Alves SH (2015) *In vitro* interaction of antifungal and antibacterial drugs against *Cryptococcus neoformans* var. *grubii* before and after capsular induction. Med Mycol 53(8):885–889. https://doi.org/10.1093/mmy/myv059

Rossato L, Loreto ÉS, Zanette RA, Chassot F, Santurio JM, Alves SH (2016) *In vitro* synergistic effects of chlorpromazine and sertraline in combination with amphotericin B against *Cryptococcus neoformans* var. *grubii*. Folia Microbiol (Praha) 61(5):399–403. https://doi.org/10.1007/s12223-016-0449-8

Sam QH, Chang MW, Chai LY (2017) The fungal mycobiome and its interaction with gut bacteria in the host. Int J Mol Sci 18(2):330. https://doi.org/10.3390/ijms18020330

Sardi Jde C, Pitangui Nde S, Rodríguez-Arellanes G, Taylor ML, Fusco-Almeida AM, Mendes-Giannini MJ (2014) Highlights in pathogenic fungal biofilms. Rev Iberoam Micol 31(1):22–29. https://doi.org/10.1016/j.riam.2013.09.014

Sasaki E, Maesaki S, Miyazaki Y, Yanagihara K, Tomono K, Tashiro T, Kohno S (2000) Synergistic effect of ofloxacin and fluconazole against azole-resistant *Candida albicans*. J Infect Chemother 6(3):151–154. https://doi.org/10.1007/s101560070014

Schwarz P, Dannaoui E (2020) *In vitro* interaction between isavuconazole and tacrolimus, cyclosporin A, or sirolimus against *Aspergillus* species. J Fungi (Basel) 6(3):103. https://doi.org/10.3390/jof6030103

Schwarz P, Schwarz PV, Felske-Zech H, Dannaoui E (2019) *In vitro* interactions between isavuconazole and tacrolimus, cyclosporin A or sirolimus against *Mucorales*. J Antimicrob Chemother 74(7):1921–1927. https://doi.org/10.1093/jac/dkz102

Sehgal SN, Baker H, Vézina C (1975) Rapamycin (AY-22,989), a new antifungal antibiotic. II. Fermentation, isolation and characterization. J Antibiot (Tokyo) 28(10):727–732. https://doi.org/10.7164/antibiotics.28.727

Shalit I, Shadkchan Y, Mircus G, Osherov N (2009) *In vitro* synergy of caspofungin with licensed and novel antifungal drugs against clinical isolates of *Fusarium* spp. Med Mycol 47(5):457–462. https://doi.org/10.1080/13693780802232910

Sharma S, Kaur H, Khuller GK (2001) Cell cycle effects of the phenothiazines: trifluoperazine and chlorpromazine in *Candida albicans*. FEMS Microbiol Lett 199(2):185–190. https://doi.org/10.1111/j.1574-6968.2001.tb10672.x

Shi W, Chen Z, Chen X, Cao L, Liu P, Sun S (2010) The combination of minocycline and fluconazole causes synergistic growth inhibition against *Candida albicans*: an *in vitro* interaction of antifungal and antibacterial agents. FEMS Yeast Res 10(7):885–893. https://doi.org/10.1111/j.1567-1364.2010.00664.x

Shiers S, Pradhan G, Mwirigi J, Mejia G, Ahmad A, Kroener S, Price T (2018) Neuropathic pain creates an enduring prefrontal cortex dysfunction corrected by the type II diabetic drug metformin but not by gabapentin. J Neurosci 38(33):7337–7350. https://doi.org/10.1523/JNEUROSCI.0713-18.2018

Shinde RB, Chauhan NM, Raut JS, Karuppayil SM (2012) Sensitization of *Candida albicans* biofilms to various antifungal drugs by cyclosporine A. Ann Clin Microbiol Antimicrob 11:27. https://doi.org/10.1186/1476-0711-11-27

Silva CR, de Andrade Neto JB, Sidrim JJ, Angelo MR, Magalhães HI, Cavalcanti BC, Brilhante RS, Macedo DS, de Moraes MO, Lobo MD, Grangeiro TB, Nobre Júnior HV (2013) Synergistic effects of amiodarone and fluconazole on *Candida tropicalis* resistant to fluconazole. Antimicrob Agents Chemother 57(4):1691–1700. https://doi.org/10.1128/AAC.00966-12

Silva THS, Araújo CV, Santos KMDC, Alves NDS, Gomes THS, Silva AKFE, Silva NCLDS, Damasceno Júnior ECB, Carvalho AMA, Mendes MGA, Caminha HB, Daboit TC, Ferreira TB, Andrade-Silva LE, Silva-Vergara ML, Ferreira-Paim K, Fonseca FM (2020) Synergic effect of simvastatin in combination with amphotericin B against environmental strains of *Cryptococcus neoformans* from northeastern Brazil: a prospective experimental study. Sao Paulo Med J 138(1):40–46. https://doi.org/10.1590/1516-3180.2019.0107.R2.16092019

Singh N, Avery RK, Munoz P, Pruett TL, Alexander B, Jacobs R, Tollemar JG, Dominguez EA, Yu CM, Paterson DL, Husain S, Kusne S, Linden P (2003) Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. Clin Infect Dis 36(1):46–52. https://doi.org/10.1086/345441

Smego RA Jr, Perfect JR, Durack DT (1984) Combined therapy with amphotericin B and 5-fluorocytosine for *Candida* meningitis. Rev Infect Dis 6(6):791–801. https://doi.org/10.1093/clinids/6.6.791

Smitherman L (2016) In brief: antifungal drugs. Pediatr Rev 37(6):267–268. https://doi.org/10.1542/pir.2015-0171

Steinbach WJ, Schell WA, Blankenship JR, Onyewu C, Heitman J, Perfect JR (2004) *In vitro* interactions between antifungals and immunosuppressants against *Aspergillus fumigatus*. Antimicrob Agents Chemother 48(5):1664–1669. https://doi.org/10.1128/aac.48.5.1664-1669.2004

Stergiopoulou T, Meletiadis J, Sein T, Papaioannidou P, Tsiouris I, Roilides E, Walsh TJ (2009) Comparative pharmacodynamic interaction analysis between ciprofloxacin, moxifloxacin and levofloxacin and antifungal agents against *Candida albicans* and *Aspergillus fumigatus*. J Antimicrob Chemother 63(2):343–348. https://doi.org/10.1093/jac/dkn473

Sugar AM, Liu XP, Chen RJ (1997) Effectiveness of quinolone antibiotics in modulating the effects of antifungal drugs. Antimicrob Agents Chemother 41(11):2518–2521. https://doi.org/10.1128/AAC.41.11.2518

Sugita T, Tajima M, Tsubuku H, Tsuboi R, Nishikawa A (2006) A new calcineurin inhibitor, pimecrolimus, inhibits the growth of *Malassezia* spp. Antimicrob Agents Chemother 50(8):2897–2898. https://doi.org/10.1128/AAC.00687-06

Sun S, Li Y, Guo Q, Shi C, Yu J, Ma L (2008) *In vitro* interactions between tacrolimus and azoles against *Candida albicans* determined by different methods. Antimicrob Agents Chemother 52(2):409–417. https://doi.org/10.1128/AAC.01070-07

Sun J, Hoying JB, Deymier PA, Zhang DD, Wong PK (2016) Cellular architecture regulates collective calcium signaling and cell contractility. PLoS Comput Biol 12(5):e1004955. https://doi.org/10.1371/journal.pcbi.1004955

Sun W, Wang D, Yu C, Huang X, Li X, Sun S (2017) Strong synergism of dexamethasone in combination with fluconazole against resistant *Candida albicans* mediated by inhibiting drug efflux and reducing virulence. Int J Antimicrob Agents 50(3):399–405. https://doi.org/10.1016/j.ijantimicag.2017.03.015

Tashiro M, Kimura S, Tateda K, Saga T, Ohno A, Ishii Y, Izumikawa K, Tashiro T, Kohno S, Yamaguchi K (2012) Pravastatin inhibits farnesol production in *Candida albicans* and improves survival in a mouse model of systemic candidiasis. Med Mycol 50(4):353–360. https://doi.org/10.3109/13693786.2011.610037

Theken KN, Grosser T (2018) Weight-adjusted aspirin for cardiovascular prevention. Lancet 392(10145):361–362. https://doi.org/10.1016/S0140-6736(18)31307-2

Thomas S, Izard J, Walsh E, Batich K, Chongsathidkiet P, Clarke G, Sela DA, Muller AJ, Mullin JM, Albert K, Gilligan JP, DiGuilio K, Dilbarova R, Alexander W, Prendergast GC (2017) The host microbiome regulates and maintains human health: a primer and perspective for non-microbiologists. Cancer Res 77(8):1783–1812. https://doi.org/10.1158/0008-5472.CAN-16-2929

Torre-Cisneros J, Mañez R, Kusne S, Alessiani M, Martin M, Starzl TE (1991) The spectrum of aspergillosis in liver transplant patients: comparison of FK506 and cyclosporine immunosuppression. Transplant Proc 23(6):3040–3041

Treviño-Rangel Rde J, Villanueva-Lozano H, Hernández-Rodríguez P, Martínez-Reséndez MF, García-Juárez J, Rodríguez-Rocha H, González GM (2016) Activity of sertraline against *Cryptococcus neoformans*: *in vitro* and *in vivo* assays. Med Mycol 54(3):280–286. https://doi.org/10.1093/mmy/myv109

Treviño-Rangel RJ, Villanueva-Lozano H, Méndez-Galomo KS, Solís-Villegas EM, Becerril-García MA, Montoya AM, Robledo-Leal ER, González GM (2019) *In vivo* evaluation of the antifungal activity of sertraline against *Aspergillus fumigatus*. J Antimicrob Chemother 74(3):663–666. https://doi.org/10.1093/jac/dky455

Tseng CH (2015) Metformin reduces ovarian cancer risk in Taiwanese women with type 2 diabetes mellitus. Diabetes Metab Res Rev 31(6):619–626. https://doi.org/10.1002/dmrr.2649

Uppuluri P, Nett J, Heitman J, Andes D (2008) Synergistic effect of calcineurin inhibitors and fluconazole against *Candida albicans* biofilms. Antimicrob Agents Chemother 52(3):1127–1132. https://doi.org/10.1128/AAC.01397-07

Vazquez JA (2005) Anidulafungin: a new echinocandin with a novel profile. Clin Ther 27(6):657–673. https://doi.org/10.1016/j.clinthera.2005.06.010

Venturini T, Rossato L, Chassot F, Tairine Keller J, Baldissera Piasentin F, Morais Santurio J, Hartz Alves S (2016) *In vitro* synergistic combinations of pentamidine, polymyxin B, tigecycline and tobramycin with antifungal agents against *Fusarium* spp. J Med Microbiol 65(8):770–774. https://doi.org/10.1099/jmm.0.000301

Vermes A, Guchelaar HJ, Dankert J (2000) Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. J Antimicrob Chemother 6(2):171–179. https://doi.org/10.1093/jac/46.2.171

Vézina C, Kudelski A, Sehgal SN (1975) Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing *streptomycete* and isolation of the active principle. J Antibiot (Tokyo) 28(10):721–726. https://doi.org/10.7164/antibiotics.28.721

Vitale RG, Afeltra J, Meis JF, Verweij PE (2007) Activity and post antifungal effect of chlorpromazine and trifluopherazine against *Aspergillus*, *Scedosporium* and zygomycetes. Mycoses 50(4):270–276. https://doi.org/10.1111/j.1439-0507.2007.01371.x

Wang Y, Casadevall A (1996) Susceptibility of melanized and nonmelanized *Cryptococcus neoformans* to the melanin-binding compounds trifluoperazine and chloroquine. Antimicrob Agents Chemother 40(3):541–545. https://doi.org/10.1128/AAC.40.3.541

Westermeyer C, Macreadie IG (2007) Simvastatin reduces ergosterol levels, inhibits growth and causes loss of mtDNA in *Candida glabrata*. FEMS Yeast Res 7(3):436–441. https://doi.org/10.1111/j.1567-1364.2006.00194.x

Wiederhold NP (2017) Antifungal resistance: current trends and future strategies to combat. Infect Drug Resist 10:249–259. https://doi.org/10.2147/IDR.S124918

Wiederhold NP (2018) The antifungal arsenal: alternative drugs and future targets. Int J Antimicrob Agents 51(3):333–339. https://doi.org/10.1016/j.ijantimicag.2017.09.002

Wood NC, Nugent KM (1985) Inhibitory effects of chlorpromazine on *Candida* species. Antimicrob Agents Chemother 27(5):692–694. https://doi.org/10.1128/aac.27.5.692

Wu Y, Totten M, Memon W, Ying C, Zhang SX (2020) *In vitro* antifungal susceptibility of the emerging multidrug-resistant pathogen *Candida auris* to miltefosine alone and in combination with amphotericin B. Antimicrob Agents Chemother 64(2):e02063–e02019. https://doi.org/10.1128/AAC.02063-19

Yang S, Liao Y, Cong L, Lu X, Yang R (2016) *In vitro* interactions between non-steroidal anti-inflammatory drugs and antifungal agents against planktonic and biofilm forms of *Trichosporon asahii*. PLoS One 11(6):e0157047. https://doi.org/10.1371/journal.pone.0157047

Yang J, Gao L, Yu P, Kosgey JC, Jia L, Fang Y, Xiong J, Zhang F (2019) *In vitro* synergy of azole antifungals and methotrexate against *Candida albicans*. Life Sci 235:116827. https://doi.org/10.1016/j.lfs.2019.116827

Yousfi H, CASsagne C, Ranque S, Rolain JM, Bittar F (2019) Repurposing of ribavirin as an adjunct therapy against invasive *Candida* strains in an *in vitro* study. Antimicrob Agents Chemother 63(10):e00263–e00219. https://doi.org/10.1128/AAC.00263-19

Yu Q, Ding X, Xu N, Cheng X, Qian K, Zhang B, Xing L, Li M (2013) *In vitro* activity of verapamil alone and in combination with fluconazole or tunicamycin against *Candida albicans* biofilms. Int J Antimicrob Agents 41(2):179–182. https://doi.org/10.1016/j.ijantimicag.2012.10.009

Yu Q, Ding X, Zhang B, Xu N, Jia C, Mao J, Zhang B, Xing L, Li M (2014a) Inhibitory effect of verapamil on *Candida albicans* hyphal development, adhesion and gastrointestinal colonization. FEMS Yeast Res 14(4):633–641. https://doi.org/10.1111/1567-1364.12150

Yu Q, Xiao C, Zhang K, Jia C, Ding X, Zhang B, Wang Y, Li M (2014b) The calcium channel blocker verapamil inhibits oxidative stress response in *Candida albicans*. Mycopathologia 177(3-4):167–177. https://doi.org/10.1007/s11046-014-9735-7

Zeidler U, Bougnoux ME, Lupan A, Helynck O, Doyen A, Garcia Z, Sertour N, Clavaud C, Munier-Lehmann H, Saveanu C, d'Enfert C (2013) Synergy of the antibiotic colistin with echinocandin antifungals in *Candida* species. J Antimicrob Chemother 68(6):1285–1296. https://doi.org/10.1093/jac/dks538

Zeng Q, Zhang Z, Chen P, Long N, Lu L, Sang H (2019) *In vitro* and *in vivo* efficacy of a synergistic combination of itraconazole and verapamil against *Aspergillus fumigatus*. Front Microbiol 10:1266. https://doi.org/10.3389/fmicb.2019.01266

Zhai B, Zhou H, Yang L, Zhang J, Jung K, Giam CZ, Xiang X, Lin X (2010) Polymyxin B, in combination with fluconazole, exerts a potent fungicidal effect. J Antimicrob Chemother 65(5):931–938. https://doi.org/10.1093/jac/dkq046

Zhang J, Heitman J, Chen YL (2012) Comparative analysis of calcineurin signaling between *Candida dubliniensis* and *Candida albicans*. Commun Integr Biol 5(2):122–126. https://doi.org/10.4161/cib.18833

Zhang M, Yan H, Lu M, Wang D, Sun S (2020) Antifungal activity of ribavirin used alone or in combination with fluconazole against *Candida albicans* is mediated by reduced virulence. Int J Antimicrob Agents 55(1):105804. https://doi.org/10.1016/j.ijantimicag.2019.09.008

Zhao YJ, Khoo AL, Tan G, Teng M, Tee C, Tan BH, Ong B, Lim BP, Chai LY (2016) Network meta-analysis and pharmacoeconomic evaluation of fluconazole, itraconazole, posaconazole, and voriconazole in invasive fungal infection prophylaxis. Antimicrob Agents Chemother 60(1):376–386. https://doi.org/10.1128/AAC.01985-15

Zhou Y, Yang H, Zhou X, Luo H, Tang F, Yang J, Alterovitz G, Cheng L, Ren B (2018) Lovastatin synergizes with itraconazole against planktonic cells and biofilms of *Candida albicans* through the regulation on ergosterol biosynthesis pathway. Appl Microbiol Biotechnol 102(12):5255–5264. https://doi.org/10.1007/s00253-018-8959-8