Drug repurposing strategies in the discovery of antifungal agents

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Abstract: The morbidity and mortality caused by invasive fungal infections is 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 an effective way of expanding the application of existing drugs. In the last years, various existing drugs have been shown to be useful in the prevention and treatment of the 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.

Keywords: drug repurposing; antifungal therapy; antifungal mechanism; clinical application; antifungal agent

1.   Introduction

Fungal infection has become a significant event leading to over 1.5 million deaths annually worldwide [1]. To date, the most common fungal infections related to human mortality and morbidity are caused by *Cryptococcus*, *Candida*, and *Aspergillus* [2]. The impact of mycoses has increased due to developments in transplant surgery, chemoradiotherapy, hemodialysis, and the use of immunosuppressive agents, especially in patients with immunodeficiency disorders, with an estimated mortality ranging from 35 % to 45 % [3]. 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 [4]. In 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 % [5].

Currently, the first-line antifungal agents for invasive fungal infections are voriconazole, itraconazole, amphotericin B, and echinocandins [6]. 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, the development of old drugs to change the use or form of fungal disease, and an association between known antifungal drugs and non-antifungal agents [7]. Drug repurposing is an established strategy for the treatment of invasive fungal infections due 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 had been used in the clinic to treat non-mycotic infections are highlighted.

1.   Current antifungal drugs used in the clinic

Since the first active antimycotic griseofulvin was recognized in 1939, a multitude of antifungal agents have been used clinically. The three main types currently used in the clinic are polyenes, azoles, and echinocandins. In fungi, ergosterol, located in the cell membrane, regulates membrane structure permeability, mobility, and substance transportation by making direct linkages with the phospholipid membrane [8]. The representative polyene drug is amphotericin B, which can bind to ergosterol from lipid bilayers and form large and extramembranous aggregates [8]. These extramembranous aggregates lead to the formation of transmembraneal pores, which can leak cellular components. This results in the death of pathogenic fungi [8]. As the "gold standard" for combating invasive fungal infections for decades, amphotericin B has a broad spectrum of antifungal activity against yeasts and molds [9]. For instance, an investigation of 78 *Candida spp.* clinical strains, showed that all examined free-living cells, were susceptible to amphotericin B [10]. When amphotericin B was combined with caspofungin and voriconazole in *Aspergillus* species, the

fractional inhibitory concentration (FIC) index was only 0.10-0.22 [11]. However, it has limited clinical applications due to toxicity, which includes nephrotoxicity and infusion-related reactions such as chest pain, dyspnea, hypoxia, flushing, and urticaria [12]. 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 [9]. Toxicity was greatly reduced using these formulations; however, the results were disappointing due to their low permeability at therapeutic concentration [13].

Due to the safety and wide availability, the azoles (including fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole) are the most widely used antifungal agents, and can be used against the majority of fungi as they inhibit the cytochrome P450-dependent enzyme 14α demethylase (Cyp51) [14]. Lanosterol generating into ergosterol was blocked when azole inhibited the Cyp51.The sterol intermediates can also promote accumulated toxicity [15]. The azoles have typical fungicidal effects on molds and are fungistatic in yeasts [16]. For example, voriconazole is an effective frontline therapy for invasive aspergillosis, and the curative rate was 52.8 % in a randomized trial [17]. However, the extensive use of azoles has subsequently led to the emergence of acquired azole resistance, particularly in *Aspergillus* species [18]. A resistance rate of 26 % was found in *A. fumigatus* culture-positive patients in the ICU [19]. Azoles can also bind to the human cytochrome P450 enzyme system (CYP450), leading to reduced antifungal efficiency [20].

Echinocandins are a group of effective antifungal agents which are, according to current international guidelines, useful for the primary treatment of invasive candidiasis [21]. Anidulafungin, caspofungin, and micafungin are representatives of this group [22]. Compared with amphotericin B and fluconazole, echinocandins rarely cause resistance, have a good safety profile, 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 therapeutic concentration of 2 µg/mL caspofungin significantly decreased the metabolism of *C. albicans* and *C. parapsilosis* yeasts without or with the biofilm [23]. 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 [24,25]. 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 in the treatment of oesophageal candidiasis and candidemia compare with fluconazole [26]. 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* [27]. 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 [28]. In addition, *C. neoformans* is naturally resistant to echinocandins, which are completely ineffective in

79   treating cryptococcosis [29]. Additionally, due to their characteristic large molecular weight, low

80   oral bioavailability, and limited absorption in the gastrointestinal tract, these drugs are only

81   administered intravenously.

82   Azole resistance among *Candida* species such as *C. auris* and *Aspergillus* species*,* as well as

83   echinocandin resistance in *C. glabrata* is an alarming problem [18]. In addition, other molds such

84   as *Scedosporium* and *Fusarium* species have reduced susceptibility to clinically available antifungal

85   drugs [18]. Although amphotericin B is recognized to have excellent antifungal activity, there are

86   still fungi, such as *Candida lusitaniae* and *Aspergillus terreus* that show intrinsic resistance to

87   amphotericin B [30]. Consequently, the development of new antifungals is needed to resolve this

88   issue.

89   **2.   Drug repurposing strategy**

90   With the changes in infection disease spectra and a clearer mechanism of disease, the strategy of

91   drug repurposing to tap into new applications of existing drugs, requires innovative clinical in-depth

92   investigation of pharmacological mechanisms. A large number of drugs with new indications have

93   emerged. For example, aspirin, a traditional drug with analgesic and antipyretic activity initially,

94   and is now gradually being used in the prevention and treatment of multi-system disease that

95   involves cardiovascular disease, stroke, and digestive tract cancers [31-34]. Vitamin D is widely

96   used to regulate calcium and phosphate metabolism for bone health [35]. Recent studies have found

97   that vitamin D deficiency is associated with an increased risk of cardiovascular disease, diabetes,

98   hypercholesterolemia, and even the COVID-19 [36,37]. Metformin, originally used to treat diabetes,

99   has so far more than a dozen potential new functions including the treatment and prevention of

100 cancer, cardiovascular disease, and mental illness such as infantile autism and cognitive disorder

101 [38-44].In addition, drug repurposing is also very significant in the development of new antifungal

102 drugs, the effectiveness of existing drugs with antifungal activity have been associated with exciting

103 non-antifungal agents chiefly consisting of antibacterial drugs, immunosuppressants, statins,

104 antiarrhythmic drugs, antipsychotic drugs, antidepressant drugs, and non-steroidal anti-

105 inflammatory drugs (NSAIDs).

106 *3.1. Antibacterial drugs*

107 The discovery of antibacterial drugs has been the greatest invention of medical science in reducing

108 morbidity and mortality, and these drugs are mainly composed of tetracyclines (e.g., minocycline

109 and doxycycline), aminoglycosides (e.g., gentamicin, neomycin, paromomycin, ribostamycin, and

110 streptomycin), and quinolone polypeptides (e.g., moxifloxacin and gatifloxacin). Traditionally,

111 antibacterial drugs were commonly used as medical treatments for infectious diseases caused by

112 gram-negative bacteria, gram-positive bacteria, mycoplasma, chlamydia, rickettsia, as well as

113 spirochaetes. A number of reports have revealed that antibacterial drugs also have broad-spectrum

114 antifungal activity (Table 1). In general, they are commonly used alone or in combination to regulate

115 the gene expression levels of adhesion, hypha, or biofilm formation, to decrease extracellular glycan

116 level and cell surface hydrophobicity, and even to inhibit efflux pump activity. In *Fusarium spp*.,

117 tobramycin alone has 80 % activity and a 76 % synergistic effect with amphotericin B or

118   voriconazole, respectively, and increases the permeability of the cell wall and cell membrane of
119   fungi when combined with antifungal agents [45]. Similar findings have also been confirmed for
120   polymyxin B which mainly combines with ketoconazole, micafungin, and amphotericin B in *C.*
121   *albicans* to alter the permeability of the cell membrane [46]. Moreover, polymyxin B can integrate
122   anionic lipids on the fungal membrane both alone and combined with fluconazole with a minimum
123   concentration 8 μg/mL for *Fusarium spp., C. neoformans, Rhizopus oryzae,* and *A. fumigatus*, which
124   destroys the membrane integrity [45,47].

125   Biofilms represent one of the major virulence factors in pathogenic fungi, which develop on
126   the surfaces of stents, shunts, prostheses, implants, endotracheal tubes, pacemakers, and various
127   types of catheters [48]. Compared to planktonic cells, the interior biofilm cells display severe
128   resistance to a wide variety of clinical antifungal agents. A small subset of yeast cells in *C. albicans*
129   biofilms, were found to be highly resistant to amphotericin B. This resistance was independent of
130   the upregulation of efflux pumps and cell membrane composition [48]. When combined with
131   clarithromycin, the permeability barrier of the biofilm matrix was altered, which resulted in
132   increased penetration of amphotericin B [49]. In addition, doxycycline, tigecycline, and rifampicin
133   were also found to enhance the activity of amphotericin B to suppress biofilm formation [45, 49-
134   54].

135   Thus, antibacterial drugs have potential antifungal value due to their good antifungal activity.
136   However, human health is based on the balance of microbiota [55,56]. Although antibacterial drugs
137   have been approved for the treatment of invasive fungal infections, many problems still need to be
138   considered. For instance, antibiotic treatment will reduce the composition of colonized microbiota
139   [57]. Moreover, many antimicrobial drugs can promote fungal growth and enhance fungal
140   pathogenicity indirectly by disrupting the microbiome and eliminating anaerobic bacteria, which
141   might inhibit fungi, especially in the gut [57]. Our previous investigation (unpublished article) also
142   showed that the antifungal applications of antibiotics interfere with the homeostasis of symbiotic
143   bacteria and fungi in the body. Moreover, dysbiosis of microbiota is responsible for the occurrence
144   of many other diseases in humans such as cardiovascular, cancer, allergy, and the microbiota also
145   affect the human immune system and the synthesis of nutrients [58,59]. In addition, the
146   pharmacokinetics of antibiotics with antifungal activity *in vivo* also require further investigation.

147   *3.2. Immunosuppressants*

148   Immunosuppressants are another example of drug repurposing due to their antifungal activity. It is
149   known that immunosuppressants mainly include calcineurin inhibitors (e.g., cyclosporine;
150   tacrolimus, FK506; and pimecrolimus), target of rapamycin inhibitors (e.g., rapamycin), anti-
151   metabolic agents (e.g., mycophenolic acid, MPA; mizoribine, MZP), and glucocorticoids (e.g.,
152   hydrocortisone, budesonide, and dexamethasone). Initially, rapamycin was found to be an antifungal
153   agent and inhibited yeasts including *C. albicans*, *dermatophytes*, *Microsporum gypseum*, and
154   *Trichophyton granulosum* [75]. Rapamycin, probably acting on the recombinant FK506 binding
155   protein (FKBP) complex, showed activity on clinical isolates of *Candida* compared with candicidin,
156   nystatin, and amphotericin B in an *in vitro* investigation [76]. The immunosuppressants found to

157   have antifungal ability are briefly summarized in Table 2.

158   Inosine monophosphate dehydrogenase (IMPDH), is a crucial enzyme in *de novo* guanine
159   nucleotide biosynthesis, and plays an important role in the rapid proliferation of cells [77]. A recent
160   investigation found that benzo[b]thiophene 1,1-dioxide, an IMPDH inhibitor, can weaken the
161   virulence of *C. neoformans* or kill it entirely [78]. In addition, MPA and MZP, other types of IMPDH
162   inhibitors, were confirmed to have significant antifungal effects in *C. albicans* and *C. neoformans*
163   by disrupting *de novo* GTP biosynthesis [79-81]. Ribavirin, an antiviral agent, is also a type of
164   IMPDA inhibitor. Interestingly, it was found that ribavirin displayed potent antifungal activity in *C.*
165   *albicans* in monotherapy or in combination with fluconazole, itraconazole, and posaconazole *in*
166   *vitro* and *in vivo*. The antifungal mechanism involves disruption of vacuolar function and the
167   reduction of extracellular phospholipase activity [82, 83].

168   Calcineurin, a conserved serine-threonine specific phosphatase, consists of a catalytic subunit
169   and a regulatory subunit [84, 85]. It is one of the important mediators in calcium signals and is
170   involved in hyphal/mycelium formation in *C. neoformans* and *A. fumigatus* [86]. Clinical experience
171   has suggested that calcineurin inhibitors (cyclosporin A and FK506) can decrease the mortality of
172   invasive *Aspergillosis* by forming protein-drug complexes [87,88]. Glucocorticoids, such as
173   hydrocortisone, budesonide, and dexamethasone, are immunosuppressants with antifungal activity
174   [89-91]. However, the antifungal activity of glucocorticoids remains controversial. For instance, an
175   investigation found that hydrocortisone enhanced the growth of *Aspergillus spp.* [92].
176   Betamethasone, one of the glucocorticoids, is also capable of promoting hyphal formation,
177   stimulating extracellular phospholipase production, and decreasing the anti-*C. albicans* activity of
178   amphotericin B and nystatin [93]. Moreover, an *in vivo* investigation also found that glucocorticoids
179   increased fungal burden in the gastrointestinal tract in rats [94], and enhanced the frequency of
180   fungal translocation in mice [95]. Thus, the practical application of glucocorticoids in fungal
181   infections requires further investigation.

182   Immunosuppressant-treated fungal cells show phenotypes consistent with inhibition of planktonic
183   cell growth, morphological transformation, and biofilm formation [96, 97]. However, at present, the
184   exact mechanisms of immunosuppressant synergism with various antifungal drugs have not been
185   delineated. In particular, the TOR as a representative target may be a promising antifungal approach.
186   To date, there are no relevant fungal-specific inhibitors available [98]. On the other hand, the use of
187   immunosuppressants can inhibit the host immune response, which increases the risk of fungal
188   infection. According to a large number of *in vitro* antifungal experiments, immunosuppressants do
189   have potent antifungal effects. However, there are no clinical studies to demonstrate whether
190   immunosuppressants have antifungal effects in humans.

191   *3.3. Statins*

192   Statins are firstly known as lipid-lowering and cholesterol-lowering drugs as they inhibit HMG-
193   CoA reductase (an essential enzyme in cholesterol biosynthesis) [114], and are classified according
194   to their hydrophobicity into hydrophilic statins (pravastatin and rosuvastatin) and lipophilic statins
195   (atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin). It has been

196 confirmed that statins exert a broad spectrum of anti-fungal effects on *Candida spp.*, *Aspergillus*
197 *spp.*, and Zygomycetes [115]. Table 3 shows a brief summary of the statins with antifungal ability.
198 The antifungal mechanism of statins is focused primarily on the biofilm. For example, the changes
199 in the main components of the biofilm or genes associated with fungal biofilm formation following
200 monotherapy or/and synergism of antifungal agents have been verified. Inexplicably, antifungal
201 activity findings are inconsistent. For instance, pravastatin has synergistic effects with fluconazole
202 by inhibiting farnesol production against *C. albican*s [116], and in contrast, no synergy was found
203 between pravastatin and fluconazole *in vitro* in another investigation [117]. In addition, a study even
204 reported that pravastatin did not inhibit the growth of *Candida spp*. [118]. The reason for this may
205 be due to differences in fungi strains, and different methodology. These contradictory findings
206 require clarification in further investigations.

207 *3.4. Antiarrhythmic drugs*

208 Antiarrhythmic drugs, which are used in the prevention and treatment of tachycardia, bradycardia,
209 or arrhythmia, include sodium channel antagonists, β -receptor blockers, potassium channel
210 blockers (PCRs), and calcium channel blockers (CCBs). Trails have shown that amiodarone, PCRs,
211 and CCBs exhibit favorable antifungal activity when administered alone or combined with
212 conventional antifungals. CCBs, as the name suggests, prevent calcium ions entering cells and
213 maintain metabolic processes. Verapamil (verapamil hydrochloride), a phenylalkylamine CCB,
214 mainly combats *C. albicans* by affecting hyphal development, adhesion, gastrointestinal
215 colonization or increasing strain susceptibility to oxidative stress [131,132]. In addition, verapamil
216 enhances the antifungal activity of tunicamycin or fluconazole against *C. albicans* during biofilm
217 formation and pre-formed biofilms [133]. In *A. fumigatus*, the drug efflux pump was blocked and
218 ergosterol content was decreased following treatment with verapamil and itraconazole
219 simultaneously [134]. Other CCBs, such as diltiazem, nicardipine, and nifedipine, have shown
220 antifungal activity against *C. albicans, C. glabrata,* Ascomycetous and Mucoralean fungi, either
221 alone or in combination with antifungals [135-137]. Amiodarone is known to block potassium,
222 sodium and calcium channels, and is commonly used to treat and prevent tachyarrhythmia [138-
223 140]. In pathogens, amiodarone mainly disrupted calcium homeostasis to elicit high levels of
224 cytoplasmic calcium, leading to cell death in *Cryptococcus spp., Aspergillus spp., Fusarium*
225 *oxysporum, C. albicans, C. tropicalis,* and *Saccharomyces cerevisiae* [141-147]. In addition,
226 amiodarone displayed potent fungicidal effects at low dose combined with fluconazole and
227 miconazole [148]. Hence, calcium channels may be potential targets in the therapy of fungal-related
228 infections.

229 *3.5. Antipsychotic drugs*

230 Antipsychotic drugs include benzamides, butyrophenones, dibenzoxazepine, phenothiazines, and
231 thioxanthene. Phenothiazines are the first generation of antipsychotics, and are mainly used to treat
232 schizophrenia and mania. In addition, phenothiazines possess multiple effects such as altering the
233 metabolism of cyclic nucleotides, modifying the structure of membranes, binding to calmodulin and
234 they participate in many intracellular responses [149], which may explain the antifungal action of

phenothiazines [150,151]. 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.*, *C. neoformans* either alone or in combination with ketoconazole and amphotericin B [150-154]. Trifluoperazine also has fungicidal effects on *C. neoformans*, especially on melanized cells [155]. 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 [156]. The minimum fungicidal concentration of chlorpromazine and trifluoperazine in *Aspergillus spp., Scedosporium,* and *Pseudallescheria* ranged between 10 and 64 μg/mL [157,158]. 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 [159].

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 [158].

3.6. Antidepressant drugs

There are currently many types of antidepressant drugs used in the clinic. 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 [160]. SSRIs effectively inhibit the uptake of serotonin by neurons from synaptic spaces, which increase the availability of this neurotransmitter in these spaces and improves the emotional states, and treats depressive mental disorders [161]. 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 spp.* strains *in vitro* with or without fluconazole. Moreover, they also improved the survival rate of *Galleria mellonella in vivo*. The antifungal mechanism involves inhibition of extracellular phospholipase activity by down-regulated *SAP1-4* genes in resistant *C. albicans* [162,163]. 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.* [164]. In addition, fluoxetine exhibited synergistic effects against *C. albicans* biofilms and relieved oral candidiasis in infected mice when combined with caspofungin [165]. 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* [166,167]. Similar results showed that sertraline had fungistatic or fungicidal effects in *Candida spp., Coccidioides immitis, C. neoformans, Trichosporon asahii,* and *A. fumigatus* [166-171].

3.7. Non-steroidal anti-inflammatory drugs (NSAIDs)

274 NSAIDs, act mainly by inhibiting the activity of cyclooxygenase to reduce the production of
275 prostaglandins (PGs), thus have antipyretic, analgesic, anti-inflammatory, and other functions [172].
276 NSAIDs, especially aspirin, etodolac, diclofenac, celecoxib, nimesulide, ibuprofen, meloxicam,
277 ketoprofen, tenoxicam, and ketorolac exhibited favorable anti-*C. albicans* effects by inhibiting the
278 synthesis of fungal PGs, which play an important role in biofilm development, adhesion, and
279 morphogenesis in *C. albicans* [173,174]. In addition, most of these drugs had synergistic or additive
280 (ketorolac) activity with fluconazole against *C. albicans* [174]. Subsequently, the antifungal
281 mechanisms of aspirin and ibuprofen have become clearer. They can, by activating the high-
282 osmolarity glycerol pathway, induce the accumulation of reactive oxygen species (ROS), and then
283 simultaneously damage the integrity of cell membranes leading to the death of *Cryptococcus* cells
284 [175]. In addition, aspirin and ibuprofen combined with fluconazole, caspofungin, and amphotericin
285 B have effects on fungi [175,176]. Ibuprofen also has anti-*Sporothrix* activity singly (median MIC
286 of 256 μg/mL) or in combination with antifungal agents including amphotericin B, itraconazole, and
287 terbinafine [177]. Diclofenac sodium can down-regulate the expression of *Ef-1* gene, which is
288 involved in cellular RNA transport, cell cycle, and apoptosis [178], thus resulting in a reduction in
289 the formation of *A. fumigatus* filaments [179].

290 **4. Conclusion**

291 In this review, we summarized the antifungal effects of a number of non-antifungal agents. In
292 addition, some antitumor agents such as miltefosine [180], tamoxifen [181], methotrexate, [182]
293 and antiepileptic drugs [183] have also been reported to have antifungal effects. The use of drug
294 repurposing strategies in the discovery of novel antifungal agents is a revelation in the identification
295 of new antifungal drugs through structural readjustment. With regard to their related antifungal
296 targets, there are still many antifungal mechanisms of the above-mentioned drugs which are unclear
297 (Fig. 1). To reveal the precise targets, further investigations should be performed using transcriptome
298 analysis and molecular techniques, which will lay the foundation for the development of novel
299 antifungal drugs for example using target design. In addition, these antifungal experiments have
300 only focused on either *in vitro* studies or animal model experiments. There is not enough clinical
301 evidence to prove their practical use in the clinic. Moreover, many factors, such as changes in
302 medium composition will perhaps lead to different or completely opposite results. *In vivo* studies,
303 differences between animal models or homogeneous animal models and differences in
304 pharmacokinetic and pharmacodynamic parameters of compounds in these models, and the effects
305 of host-derived serum and, cellular factors should be clarified. Hence, it is essential to use systematic
306 and standard research approaches, as well as collect more clinical data to evaluate the antifungal
307 effectiveness of these agents.

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Reference

1. Deaguero IG.; Huda MN.; Rodriguez V.; Zicari J.; Al-Hilal TA.; Badruddoza AZM.; Nurunnabi M. Nano-vesicle based anti-fungal formulation shows higher stability, skin diffusion, biosafety and anti-fungal efficacy *in vitro*. *Pharmaceutics*. **2020**, *12*, 516.

2. Boral H.; Metin B.; Döğen A.; Seyedmousavi S.; Ilkit M. Overview of selected virulence attributes in *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton rubrum*, and *Exophiala* dermatitidis. *Fungal Genet Biol*. **2018**, *111*, 92-107.

3. Drgona L.; Khachatryan A.; Stephens J.; Charbonneau C.; Kantecki M.; Haider S.; Barnes R. 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*. **2014**, *33*, 7-21.

4. Du H.; Bing J.; Hu T.; Ennis CL.; Nobile CJ.; Huang G. *Candida auris*: epidemiology, biology, antifungal resistance, and virulence. *PLoS Pathog*. **2020**, *16*, e1008921.

5. Chowdhary A.; Tarai B.; Singh A.; Sharma A. Multidrug-resistant *Candida auris* infections in critically ill coronavirus disease patients, India, April-July 2020. *Emerg Infect Dis*. **2020**, *26*, 2694-2696.

6. Zhao Y J.; Khoo A L.; Tan G.; Teng M.; Tee C.; Tan B H.; Ong B.; Lim B P.; Chai L Y A. Network meta-analysis and pharmacoeconomic evaluation of fluconazole, itraconazole, posaconazole, and voriconazole in invasive fungal infection prophylaxis. *Antimicrobial Agents and Chemotherapy*. **2016**, *60*, 376-386.

7. Robbins N.; Wright GD.; Cowen LE. Antifungal drugs: the current armamentarium and development of new agents. *Microbiol Spectr*. **2016**, *4*, 5.

8. 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. Amphotericin forms an extramembranous and fungicidal sterol sponge. *Nat Chem Biol*. **2014**, *10*, 400-6.

9. Ostrosky-Zeichner L.; Marr K A.; Rex J H.; Cohen S H. Amphotericin B: time for a new "gold standard". *Clin Infect Dis*. **2003**, *37*, 415-425.

10. Prazynska M.; Gospodarek E. *In vitro* effect of amphotericin B on *Candida albicans*, *Candida glabrata* and *Candida parapsilosis* biofilm formation. *Mycopathologia*. **2014**, *177*, 19-27.

11. O'shaughnessy E M.; Meletiadis J.; Stergiopoulou T.; Demchok J P.; Walsh T J. Antifungal interactions within the triple combination of amphotericin B, caspofungin and voriconazole against *Aspergillus* species. *J Antimicrob Chemother*. **2006**, *58*, 1168-1176.

12. Roden M M.; Nelson L D.; Knudsen T A.; Jarosinski P F.; Starling J M.; Shiflett S E.; Calis K.; Dechristoforo R.; Donowitz G R.; Buell D.; Walsh T J. Triad of acute infusion-related reactions associated with liposomal amphotericin B: analysis of clinical and epidemiological characteristics. *Clin Infect Dis*. **2003**, *36*, 1213-1220.

13. Smitherman L. In brief: antifungal drugs. *Pediatrics in Review*. **2016**, *37*, 267-268.

14.   Emami S.; Tavangar P.; Keighobadi M. An overview of azoles targeting sterol 14α-demethylase for antileishmanial therapy. *Eur J Med Chem*. **2017**, *135*, 241-259.

15.   Onyewu C.; Blankenship JR.; Del Poeta M.; Heitman J. Ergosterol biosynthesis inhibitors become fungicidal when combined with calcineurin inhibitors against *Candida albicans*, *Candida glabrata*, and *Candida krusei*. *Antimicrob Agents Chemother*. **2003**, *47*, 956-64.

16.   Perlin DS.; Rautemaa-Richardson R.; Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. *Lancet Infect Dis*. **2017**, *17*, e383-e392.

17.   Haidar G.; Singh N. How we approach combination antifungal therapy for invasive aspergillosis and mucormycosis in transplant recipients. *Transplantation*. **2018**, *102*, 1815-1823.

18.   Wiederhold NP. Antifungal resistance: current trends and future strategies to combat. *Infect Drug Resist*. **2017**, *10*, 249-259.

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

20.   Wiederhold NP. The antifungal arsenal: alternative drugs and future targets. *Int J Antimicrob Agents*. **2018**, *51*, 333-339.

21.   Chang C C.; Slavin M A.; Chen S C A. New developments and directions in the clinical application of the echinocandins. *Arch Toxicol*. **2017**, *91*, 1613-1621.

22.   Emri T.; Majoros L.; Tóth V.; Pócsi I. Echinocandins: production and applications. *Appl Microbiol Biotechnol*. **2013**, *97*, 3267-3284.

23.   Cocuaud C.; Rodier M H.; Daniault G.; Imbert C. Anti-metabolic activity of caspofungin against *Candida albicans* and *Candida parapsilosis* biofilms. *J Antimicrob Chemother*. **2005**, *56*, 507-512.

24.   Ramage G.; Vandewalle K.; Bachmann S P.; Wickes B L.; Lopez-Ribot J L. *In vitro* pharmacodynamic properties of three antifungal agents against preformed *Candida albicans* biofilms determined by time-kill studies. *Antimicrob Agents Chemother*. **2002**, *46*, 3634-3636.

25.   Garbino J. Caspofungin--a new therapeutic option for oropharyngeal candidiasis. *Clin Microbiol Infect*. **2004**, *10*, 187-189.

26.   Vazquez J A. Anidulafungin: a new echinocandin with a novel profile. *Clin Ther*. **2005**, *27*, 657-673.

27.   Gil-Alonso S.; Jauregizar N.; Eraso E.; Quindós G. Postantifungal effect of micafungin against the species complexes of *Candida albicans* and *Candida parapsilosis*. *PloS one*. **2015**, *10*, e0132730-e0132730.

28.   Perlin DS. Cell wall-modifying antifungal drugs. *Curr Top Microbiol Immunol*. **2020**, *425*, 255-275.

29.   Denning DW. Echinocandin antifungal drugs. *Lancet*. **2003**. *362*, 1142–1151.

30.   Arendrup MC.; Cuenca-Estrella M.; Lass-Flo¨rl C.; Hope WW. EUCAST technical note on *Aspergillus* and amphotericin B, itraconazole, and posaconazole. *Clin Microbiol Infect*. **2012**, *18*, E248–E250.

31.   Theken KN.; Grosser T. Weight-adjusted aspirin for cardiovascular prevention. *Lancet*. **2018**, *392*, 361-362.

32.   Johnston SC.; Amarenco P.; Denison H.; Evans SR.; Himmelmann A.; James S.; Knutsson M.; Ladenvall P.; Molina CA.; Wang Y.; THALES investigators. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med*. **2020**, *383*, 207-217.

33.   Bosetti C.; Santucci C.; Gallus S.; Martinetti M.; La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol*. **2020**, *31*, 558-568.

34.   Burn J.; Sheth H.; Elliott F.; Reed L.; Macrae F.; Mecklin JP.; Möslein G.; McRonald FE.; Bertario L.; Evans DG.; et al. 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*. **2020**, *395*, 1855-1863.

35.   Ng K, Nimeiri HS.; McCleary NJ.; Abrams TA.; Yurgelun MB.; Cleary JM.; Rubinson DA.; Schrag D.; Miksad R.; Bullock AJ.; et al. 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*. **2019**, *321*, 1370-1379.

36.   Kouvari M.; Panagiotakos DB.; Chrysohoou C.; Yannakoulia M.; Georgousopoulou EN.; Tousoulis D.; Pitsavos C.; ATTICA study investigators. Dietary vitamin D intake, cardiovascular disease and cardiometabolic risk factors: a sex-based analysis from the ATTICA cohort study. *J Hum Nutr Diet*. **2020**, *33*, 708-717.

37.   Meltzer DO.; Best TJ.; Zhang H.; Vokes T.; Arora V.; Solway J. Association of vitamin D status and other clinical characteristics with COVID-19 test results. *JAMA Netw Open*. **2020**, *3*, e2019722.

38.   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.; et al. 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.* **2019**, *5*, e192553

39.   Lee J.; Yesilkanal AE.; Wynne JP.; Frankenberger C.; Liu J.; Yan J.; Elbaz M.; Rabe DC.; Rustandy FD.; Tiwari P.; et al. Effective breast cancer combination therapy targeting BACH1 and mitochondrial metabolism. *Nature*. **2019**, *568*, 254-258.

40.   Tseng CH. Metformin reduces ovarian cancer risk in Taiwanese women with type 2 diabetes mellitus. *Diabetes Metab Res Rev*. **2015**, *31*, 619-26.

41.   Cheung KS.; Chan EW.; Wong AYS.; Chen L.; Seto WK.; Wong ICK.; Leung WK. Metformin use and gastric cancer risk in diabetic patients after helicobacter pylori eradication. *J Natl Cancer Inst*. **2019**, *111*, 484-489.

42.   M Mohan M.; Al-Talabany S.; McKinnie A.; Mordi IR.; Singh JSS.; Gandy SJ.; Baig F.; Hussain MS.; Bhalraam U.; Khan F.; et al. 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*. **2019**, *40*, 3409-3417.

43.   Dy ABC.; Tassone F.; Eldeeb M.; Salcedo-Arellano MJ.; Tartaglia N.; Hagerman R. Metformin as targeted treatment in fragile X syndrome. *Clin Genet*. **2018**, *93*, 216-222.

44.   Shiers S.; Pradhan G.; Mwirigi J.; Mejia G.; Ahmad A.; Kroener S.; Price T. Neuropathic pain creates an enduring prefrontal cortex dysfunction corrected by the type II diabetic drug metformin but not by gabapentin. *J Neurosci*. **2018**, *38*, 7337-7350.

45.   Pozzebon Venturini T.; Rossato L.; Chassot F.; Tairine Keller J.; Baldissera Piasentin F.; Morais Santurio J.; Hartz Alves S. *In vitro* synergistic combinations of pentamidine, polymyxin B, tigecycline and tobramycin with antifungal agents against *Fusarium spp*. *J Med Microbiol*. **2016**, *65*, 770-774.

46.   Moneib NA. *In-vitro* activity of commonly used antifungal agents in the presence of rifampin, polymyxin B and norfloxacin against *C. albicans*. *J Chemother*. **1995**, *7*, 525-9.

47.   Zhai B.; Zhou H.; Yang L.; Zhang J.; Jung K.; Giam CZ.; Xiang X.; Lin X. Polymyxin B, in combination with FLC, exerts a potent fungicidal effect. *J Antimicrob Chemother*. **2010**, *65*, 931-8.

48.   Sardi Jde C.; Pitangui Nde S.; Rodríguez-Arellanes G.; Taylor ML.; Fusco-Almeida AM.; Mendes-Giannini MJ. Highlights in pathogenic fungal biofilms. *Rev Iberoam Micol*. **2014**, *31*, 22-9.

49.   Del Pozo JL.; Francés ML.; Hernáez S.; Serrera A.; Alonso M.; Rubio MF. Effect of AmB alone or in combination with rifampicin or clarithromycin against *Candida* species biofilms. *Int J Artif Organs*. **2011**, *34*, 766-70.

50.   Fernández-Rivero ME.; Del Pozo JL.; Valentín A.; de Diego AM.; Pemán J.; Cantón E. Activity of AmB and ANI combined with rifampicin, clarithromycin, ethylenediaminetetraacetic acid, N-acetylcysteine, and farnesol against *C. tropicalis* biofilms. *J Fungi (Basel)*. **2017**, *3*,16.

51.   Lew MA.; Beckett KM.; Levin MJ. Antifungal activity of four tetracycline analogues against *C. albicans in vitro*: potentiation by AmB. *J Infect Dis*. **1977**, *136*, 263-70.

52.   El-Azizi M. Enhancement of the *in vitro* activity of AmB against the biofilms of *non-albicans Candida spp.* by rifampicin and doxycycline. *J Med Microbiol*. **2007**, *56(Pt 5)*, 645-649.

53.   Miceli MH.; Bernardo SM.; Lee SA. *In vitro* analyses of the combination of high-dose doxycycline and antifungal agents against *C. albicans* biofilms. *Int J Antimicrob Agents*. **2009**, *34*, 326-32.

54.   Ku TS.; Palanisamy SK.; Lee SA. Susceptibility of *C. albicans* biofilms to azithromycin, tigecycline and vancomycin and the interaction between tigecycline and antifungals. *Int J Antimicrob Agents*. **2010**, *36*, 441-6.

55.   Limon JJ.; Skalski JH.; Underhill DM. Commensal fungi in health and disease. *Cell Host Microbe*. **2017**, *22*, 156-165.

56.   Liu J.; Ran Z.; Wang F.; Xin C.; Xiong B.; Song Z. Role of pulmonary microorganisms in the development of chronic obstructive pulmonary disease. *Crit Rev Microbiol*. **2020**, *10*, 1-12.

57.   Sam QH.; Chang MW.; Chai LY. The fungal mycobiome and its interaction with gut bacteria in the host. *Int J Mol Sci*. **2017**, *18*, 330.

58.   Thomas S.; Izard J.; Walsh E.; Batich K.; Chongsathidkiet P.; Clarke G.; Sela DA.; Muller AJ.; Mullin JM.; Albert K.; et al. The host microbiome regulates and maintains human health: a primer and perspective for non-microbiologists. *Cancer Res*. **2017**, *77*, 1783-1812.

59.   Ran Z.; Liu J.; Wang F.; Xin C.; Shen X.; Zeng S.; Song Z.; Xiong B. Analysis of pulmonary microbial diversity in patients with advanced lung cancer based on high-throughput sequencing technology. *Zhongguo Fei Ai Za Zhi*. **2020**, *23*, 1031-1038.

60.   Lu M.; Yu C.; Cui X.; Shi J.; Yuan L.; Sun S. Gentamicin synergises with azoles against drug-resistant *C. albicans*. *Int J Antimicrob Agents*. **2018**, *51*, 107-114.

61.   Loreto ES.; Tondolo JS.; Pilotto MB.; Alves SH.; Santurio JM. New insights into the *in vitro* susceptibility of *Pythium insidiosum*. *Antimicrob Agents Chemother*. **2014**, *58*, 7534-7.

62.   Nguyen MH.; Clancy CJ.; Yu YC.; Lewin AS. Potentiation of antifungal activity of AmB by azithromycin against *Aspergillus* species. *Eur J Clin Microbiol Infect Dis*. **1997**, *16*, 846-8.

63.   Stergiopoulou T.; Meletiadis J.; Sein T.; Papaioannidou P.; Tsiouris I.; Roilides E.; Walsh TJ. Comparative pharmacodynamic interaction analysis between ciprofloxacin, moxifloxacin and levofloxacin and antifungal agents against *C. albicans* and *Aspergillus fumigatus*. *J Antimicrob Chemother*. **2009**, *63*, 343-8.

64.   Ozdek SC.; Miller D.; Flynn PM.; Flynn HW. *In vitro* antifungal activity of the fourth generation fluoroquinolones against *Candida* isolates from human ocular infections. *Ocul Immunol Inflamm*. **2006**, *14*, 347-51.

65.   Deren YT.; Ozdek S.; Kalkanci A.; Akyürek N.; Hasanreisoğlu B. Comparison of antifungal efficacies of moxifloxacin, liposomal AmB, and combination treatment in experimental *C. albicans* endophthalmitis in rabbits. *Can J Microbiol*. **2010**, *56*, 1-7.

66.   Sugar AM.; Liu XP.; Chen RJ. Effectiveness of quinolone antibiotics in modulating the effects of antifungal drugs. *Antimicrob Agents Chemother*. **1997**, *41*, 2518-21.

67.   Gu W.; Yu Q.; Yu C.; Sun S. *In vivo* activity of FLC/tetracycline combinations in *Galleria mellonella* with resistant *C. albicans* infection. *J Glob Antimicrob Resist*. **2018**, *13*, 74-80.

68.   Fiori A.; Van Dijck P. Potent synergistic effect of doxycycline with FLC against *C. albicans* is mediated by interference with iron homeostasis. *Antimicrob Agents Chemother*. **2012**, *56*, 3785-96.

69.   Gao Y.; Zhang C.; Lu C.; Liu P.; Li Y.; Li H.; Sun S. Synergistic effect of doxycycline and FLC against *C. albicans* biofilms and the impact of calcium channel blockers. *FEMS Yeast Res*. **2013**, *13*, 453-62.

70.   Gao Y.; Li H.; Liu S.; Zhang X.; Sun S. Synergistic effect of FLC and doxycycline against *C. albicans* biofilms resulting from calcium fluctuation and downregulation of FLC-inducible efflux pump gene overexpression. *J Med Microbiol*. **2014**, *63*, 956-961.

71.   Shi W.; Chen Z.; Chen X.; Cao L.; Liu P.; Sun S. The combination of minocycline and FLC causes synergistic growth inhibition against *C. albicans*: an *in vitro* interaction of antifungal and antibacterial agents. *FEMS Yeast Res*. **2010**, *10*, 885-93.

72.   Gao L.; Sun Y.; Yuan M.; Li M.; Zeng T. *In vitro* and *in vivo* study on the synergistic effect of minocycline and azoles against pathogenic fungi. *Antimicrob Agents Chemother*. **2020**, *64*, e00290-20.

73.   Rossato L.; Loreto ÉS.; Venturini TP.; Azevedo MI.; Weiblen C.; Botton SA.; Santurio JM.; Alves SH. *In vitro* interaction of antifungal and antibacterial drugs against *C. neoformans* var. *grubii* before and after capsular induction. *Med Mycol*. **2015**, *53*, 885-9.

74.   Lu M.; Yang X.; Yu C.; Gong Y.; Yuan L.; Hao L.; Sun S. Linezolid in combination with azoles induced synergistic effects against *C. albicans* and protected *Galleria mellonella* against experimental candidiasis. *Front Microbiol*. **2019**, *9*, 3142.

75.   Vézina C.; Kudelski A.; Sehgal SN. Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing *streptomycete* and isolation of the active principle. *J Antibiot (Tokyo)*. **1975**, *28*, 721-6.

76.   Chowdhary A.; Sharma.; Meis JF. Azole-resistant aspergillosis: epidemiology, molecular mechanisms, and treatment. *J Infect Dis*. **2017**, *216(suppl_3)*, S436-S444.

77.   Cuny GD.; Suebsuwong C.; Ray SS. Inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitors: a patent and scientific literature review (2002-2016). *Expert Opin Ther Pat*. **2017**, *27*, 677-690.

78.   Kummari LK.; Butler MS.; Furlong E.; Blundell R.; Nouwens A.; Silva AB.; Kappler U.; Fraser JA.; Kobe B.; Cooper MA.; Robertson AAB. Antifungal benzo[b]thiophene 1,1-dioxide IMPDH inhibitors exhibit pan-assay interference (PAINS) profiles. *Bioorg Med Chem*. **2018**, *26*, 5408-5419.

79.   Banerjee D.; Burkard L.; Panepinto JC. Inhibition of nucleotide biosynthesis potentiates the antifungal activity of AmB. *PLoS One*. **2014**, *9*, e87246.

80.   Köhler GA.; Gong X.; Bentink S.; Theiss S.; Pagani GM.; Agabian N.; Hedstrom L. The functional basis of mycophenolic acid resistance in *C. albicans* IMP dehydrogenase. *J Biol Chem*. **2005**, *280*, 11295-302.

81.   Morrow CA.; Valkov E.; Stamp A.; Chow EW.; Lee IR.; Wronski A.; Williams SJ.; Hill JM.; Djordjevic JT.; Kappler U.; Kobe B.; Fraser JA. *De novo* GTP biosynthesis is critical for virulence of the fungal pathogen *C. neoformans*. *PLoS Pathog*. **2012**, *8*, e1002957.

82.   Zhang M.; Yan H.; Lu M.; Wang D.; Sun S. Antifungal activity of ribavirin used alone or in combination with fluconazole against *Candida albicans* is mediated by reduced virulence. *Int J Antimicrob Agents*. **2020**, *55*, 105804.

83.   Yousfi H.; CASsagne C.; Ranque S.; Rolain JM.; Bittar F. Repurposing of ribavirin as an adjunct therapy against invasive *Candida* strains in an *in vitro* study. *Antimicrob Agents Chemother*. **2019**, *63*, e00263-19.

84. Sun J.; Hoying JB.; Deymier PA.; Zhang DD.; Wong PK. Cellular architecture regulates collective calcium signaling and cell contractility. *PLoS Comput Biol*. **2016**, *12*, e1004955.

85. Bandyopadhyay J.; Lee J.; Bandyopadhyay A. Regulation of calcineurin, a calcium/calmodulin-dependent protein phosphatase, in *C. elegans*. *Mol Cells*. **2004**, *18*, 10-6.

86. Zhang J.; Heitman J.; Chen YL. Comparative analysis of calcineurin signaling between *Candida dubliniensis* and *C. albicans*. *Commun Integr Biol*. **2012**, *5*, 122-6.

87. Singh N.; Avery RK.; Munoz P.; Pruett TL.; Alexander B.; Jacobs R.; Tollemar JG.; Dominguez EA.; Yu CM.; Paterson DL.; et al. Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. *Clin Infect Dis*. **2003**, *36*, 46-52.

88. Torre-Cisneros J.; Mañez R.; Kusne S.; Alessiani M.; Martin M.; Starzl TE. The spectrum of aspergillosis in liver transplant patients: comparison of FK506 and cyclosporine immunosuppression. *Transplant Proc*. **1991**, *23*, 3040-1.

89. Li X.; Yu C.; Huang X.; Sun S. Synergistic effects and mechanisms of budesonide in combination with FLC against resistant *C. albicans*. *PLoS One*. **2016**, *11*, e0168936.

90. Sun W.; Wang D.; Yu C.; Huang X.; Li X.; Sun S. Strong synergism of dexamethasone in combination with FLC against resistant *C. albicans* mediated by inhibiting drug efflux and reducing virulence. *Int J Antimicrob Agents*. **2017**, *50*, 399-405.

91. Ramondenc I.; Pinel C.; Ambroise-Thomas P.; Grillot R. Does hydrocortisone modify the *in vitro* susceptibility of *Aspergillus fumigatus* to ITR and AmB? *Med Mycol*. **1998**, *36*, 69-73.

92. Ng TT.; Robson GD.; Denning DW. Hydrocortisone-enhanced growth of *Aspergillus spp.*: implications for pathogenesis. *Microbiology (Reading)*. **1994**, *140 (Pt 9)*, 2475-9.

93. Jakab Á.; Emri T.; Sipos L.; Kiss Á.; Kovács R.; Dombrádi V.; Kemény-Beke Á.; Balla J.; Majoros L.; Pócsi I. Betamethasone augments the antifungal effect of menadione--towards a novel anti-*C. albicans* combination therapy. *J Basic Microbiol*. **2015**, *55*, 973-81.

94. Myerowitz RL. Gastrointestinal and disseminated candidiasis. An experimental model in the immunosuppressed rat. *Arch Pathol Lab Med*. **1981**, *105*, 138-43.

95. Maraki S.; Hajiioannou I.; Anatoliotakis N.; Plataki M.; Chatzinikolaou I.; Zoras O.; Tselentis Y.; Samonis G. Ceftriaxone and dexamethasone affecting yeast gut flora in experimental mice. *J Chemother*. **1999**, *11*, 363-6.

96. Jia W.; Zhang H.; Li C.; Li G.; Liu X.; Wei J. The calcineruin inhibitor cyclosporine a synergistically enhances the susceptibility of *C. albicans* biofilms to FLC by multiple mechanisms. *BMC Microbiol*. **2016**, *16*, 113.

97. Uppuluri P.; Nett J.; Heitman J.; Andes D. Synergistic effect of calcineurin inhibitors and fluconazole against *Candida albicans* biofilms. *Antimicrob Agents Chemother*. **2008**, *52*, 1127-32.

98. Cordeiro RA.; Macedo RB.; Teixeira CEC.; Marques FJF.; Bandeira TJPG.; Moreira JLB.; Brilhante RSN.; Rocha MFG.; Sidrim JJC. The calcineurin inhibitor cyclosporin A exhibits synergism with antifungals against *Candida parapsilosis* species complex. *J Med Microbiol*. **2014**, *63(Pt 7)*, 936-944.

99.   Marchetti O.; Moreillon P.; Glauser MP.; Bille J.; Sanglard D. Potent synergism of the combination of FLC and cyclosporine in *C. albicans*. *Antimicrob Agents Chemother*. **2000**, *44*, 2373-81.

100.   Marchetti O.; Entenza JM.; Sanglard D.; Bille J.; Glauser MP.; Moreillon P. FLC plus cyclosporine: a fungicidal combination effective against experimental endocarditis due to *C. albicans*. *Antimicrob Agents Chemother*. **2000**, *44*, 2932-8.

101.   Kontoyiannis DP.; Lewis RE.; Osherov N.; Albert ND.; May GS. Combination of CAS with inhibitors of the calcineurin pathway attenuates growth *in vitro* in *Aspergillus* species. *J Antimicrob Chemother*. **2003**, *51*, 313-6.

102.   Uppuluri P.; Nett J.; Heitman J.; Andes D. Synergistic effect of calcineurin inhibitors and FLC against *C. albicans* biofilms. *Antimicrob Agents Chemother*. **2008**, *52*, 1127-32.

103.   Shinde RB.; Chauhan NM.; Raut JS.; Karuppayil SM. Sensitization of *C. albicans* biofilms to various antifungal drugs by cyclosporine A. *Ann Clin Microbiol Antimicrob*. **2012**, *11*, 27.

104.   Schwarz P.; Schwarz PV.; Felske-Zech H.; Dannaoui E. *In vitro* interactions between ISA and tacrolimus, cyclosporin A or sirolimus against *Mucorales*. *J Antimicrob Chemother*. **2019**, *74*, 1921-1927.

105.   Kubiça TF.; Denardi LB.; Azevedo MI.; Oliveira V.; Severo LC.; Santurio JM.; Alves SH. Antifungal activities of tacrolimus in combination with antifungal agents against FLC-susceptible and FLC-resistant *Trichosporon asahii* isolates. *Braz J Infect Dis*. **2016**, *20*, 539-545.

106.   Steinbach WJ.; Schell WA.; Blankenship JR.; Onyewu C.; Heitman J.; Perfect JR. *In vitro* interactions between antifungals and immunosuppressants against *Aspergillus fumigatus*. *Antimicrob Agents Chemother*. **2004**, *48*,1664-9.

107.   High KP.; Washburn RG. Invasive aspergillosis in mice immunosuppressed with cyclosporin A, tacrolimus (FK506), or sirolimus (rapamycin). *J Infect Dis*. **1997**, *175*, 222-5.

108.   Schwarz P.; Dannaoui E. *In vitro* interaction between ISA and tacrolimus, cyclosporin A, or sirolimus against *Aspergillus* species. *J Fungi (Basel)*. **2020**, *6*, 103.

109.   Shalit I.; Shadkchan Y.; Mircus G.; Osherov N. *In vitro* synergy of CAS with licensed and novel antifungal drugs against clinical isolates of *Fusarium spp*. *Med Mycol*. **2009**;*47*, 457-62.

110.   Sun S.; Li Y.; Guo Q.; Shi C.; Yu J.; Ma L. *In vitro* interactions between tacrolimus and azoles against *C. albicans* determined by different methods. *Antimicrob Agents Chemother*. **2008**, *52*, 409-17.

111.   Sugita T.; Tajima M.; Tsubuku H.; Tsuboi R.; Nishikawa A. A new calcineurin inhibitor, pimecrolimus, inhibits the growth of *Malassezia spp*. *Antimicrob Agents Chemother*. **2006**, *50*, 2897-8.

112.   Cruz MC.; Goldstein AL.; Blankenship J.; Del Poeta M.; Perfect JR.; McCusker JH.; Bennani YL.; Cardenas ME.; Heitman J. Rapamycin and less immunosuppressive analogs are toxic to *Candida albicans* and *Cryptococcus neoformans* via FKBP12-dependent inhibition of TOR. *Antimicrob Agents Chemother*. **2001**, *45*, 3162-70.

113.   Bastidas RJ.; Shertz CA.; Lee SC.; Heitman J.; Cardenas ME. Rapamycin exerts antifungal activity *in vitro* and *in vivo* against *Mucor circinelloides* via FKBP12-dependent inhibition of Tor. *Eukaryot Cell*. **2012**, *11*, 270-81.

114.   Esfahani AN.; Golestannejad Z.; Khozeimeh F.; Dehghan P.; Maheronnaghsh M.; Zarei Z. Antifungal effect of atorvastatin against *Candida* species in comparison to fluconazole and nystatin. *Med Pharm Rep*. **2019**, *92*, 368-373.

115.   Callegari S.; McKinnon RA.; Andrews S.; de Barros Lopes MA. Atorvastatin-induced cell toxicity in yeast is linked to disruption of protein isoprenylation. *FEMS Yeast Res*. **2010**, *10*, 188-98.

116.   Tashiro M.; Kimura S.; Tateda K.; Saga T.; Ohno A.; Ishii Y.; Izumikawa K.; Tashiro T.; Kohno S.; Yamaguchi K. Pravastatin inhibits farnesol production in *Candida albicans* and improves survival in a mouse model of systemic candidiasis. *Med Mycol*. **2012**, *50*, 353-60.

117.   Nash JD.; Burgess DS.; Talbert RL. Effect of fluvastatin and pravastatin, HMG-CoA reductase inhibitors, on fluconazole activity against *Candida albicans*. *J Med Microbiol*. **2002**, *51*,105-109.

118.   Brilhante RS.; Caetano EP.; Oliveira JS.; Castelo-Branco Dde S.; Souza ER.; Alencar LP.; Cordeiro Rde A.; Bandeira Tde J.; Sidrim JJ.; Rocha MF. Simvastatin inhibits planktonic cells and biofilms of *Candida* and *Cryptococcus* species. *Braz J Infect Dis*. **2015**, *19*, 459-65.

119.   Nyilasi I.; Kocsubé S.; Krizsán K.; Galgóczy L.; Pesti M.; Papp T.; Vágvölgyi C. *In vitro* synergistic interactions of the effects of various statins and azoles against some clinically important fungi. *FEMS Microbiol Lett*. **2010**, *307*, 175-84.

120.   Zhou Y.; Yang H.; Zhou X.; Luo H.; Tang F.; Yang J.; Alterovitz G.; Cheng L.; Ren B. Lovastatin synergizes with itraconazole against planktonic cells and biofilms of *Candida albicans* through the regulation on ergosterol biosynthesis pathway. *Appl Microbiol Biotechnol*. **2018**, *102*, 5255-5264.

121.   Chamilos G.; Lewis RE.; Kontoyiannis DP. Lovastatin has significant activity against zygomycetes and interacts synergistically with VRC. *Antimicrob Agents Chemother*. **2006**, *50*, 96-103.

122.   Westermeyer C.; Macreadie IG. Simvastatin reduces ergosterol levels, inhibits growth and causes loss of mtDNA in *C. glabrata*. *FEMS Yeast Res*. **2007**, *7*, 436-41.

123.   Cabral ME.; Figueroa LI.; Fariña JI. Synergistic antifungal activity of statin-azole associations as witnessed by *Saccharomyces cerevisiae*- and *Candida utilis*-bioassays and ergosterol quantification. *Rev Iberoam Micol*. **2013**, *30*, 31-8.

124.   Silva THS.; Araújo CV.; Santos KMDC.; Alves NDS.; Gomes THS.; Silva AKFE.; Silva NCLDS.; Damasceno Júnior ECB.; Carvalho AMA.; Mendes MGA.; et al. 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*. **2020**, *138*, 40-46.

125. Ajdidi A.; Sheehan G.; Abu Elteen K.; Kavanagh K. Assessment of the *in vitro* and *in vivo* activity of atorvastatin against *Candida albicans*. *J Med Microbiol*. **2019**, *68*, 1497-1506.

126. Lima WG.; Alves-Nascimento LA.; Andrade JT.; Vieira L.; de Azambuja Ribeiro RIM.; Thomé RG.; Dos Santos HB.; Ferreira JMS.; Soares AC. Are the statins promising antifungal agents against invasive candidiasis? *Biomed Pharmacother*. **2019**, *111*, 270-281.

127. 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. Atorvastatin as a promising anticryptococcal agent. *Int J Antimicrob Agents*. **2017**, *49*, 695-702.

128. Chin NX.; Weitzman I.; Della-Latta P. *In vitro* activity of fluvastatin, a cholesterol-lowering agent, and synergy with fluconazole and ITR against *Candida* species and *C. neoformans*. *Antimicrob Agents Chemother*. **1997**, *41*, 850-2.

129. Eldesouky HE.; Salama EA.; Li X.; Hazbun TR.; Mayhoub AS.; Seleem MN. Repurposing approach identifies pitavastatin as a potent azole chemosensitizing agent effective against azole-resistant *Candida* species. *Sci Rep*. **2020**, *10*, 7525.

130. Ajdidi A.; Sheehan G.; Kavanagh K. Exposure of *Aspergillus fumigatus* to atorvastatin leads to altered membrane permeability and induction of an oxidative stress response. *J Fungi (Basel)*. **2020**, *6*, 42.

131. Yu Q.; Ding X.; Zhang B.; Xu N.; Jia C.; Mao J.; Zhang B.; Xing L.; Li M. Inhibitory effect of verapamil on *C. albicans* hyphal development, adhesion and gastrointestinal colonization. *FEMS Yeast Res*. **2014**, *14*, 633-41.

132. Yu Q.; Xiao C.; Zhang K.; Jia C.; Ding X.; Zhang B.; Wang Y.; Li M. The calcium channel blocker verapamil inhibits oxidative stress response in *C. albicans*. *Mycopathologia*. **2014**, *177*, 167-77.

133. Yu Q.; Ding X.; Xu N.; Cheng X.; Qian K.; Zhang B.; Xing L.; Li M. *In vitro* activity of verapamil alone and in combination with FLC or tunicamycin against *C. albicans* biofilms. *Int J Antimicrob Agents*. **2013**, *41*, 179-82.

134. Zeng Q.; Zhang Z.; Chen P.; Long N.; Lu L.; Sang H. *In vitro* and *in vivo* efficacy of a synergistic combination of ITR and verapamil against *Aspergillus fumigatus*. *Front Microbiol*. **2019**, *10*,1266.

135. Alnajjar LM.; Bulatova NR.; Darwish RM. Evaluation of four calcium channel blockers as FLC resistance inhibitors in *C. glabrata*. *J Glob Antimicrob Resist*. **2018**, *14*, 185-189.

136. Homa M.; Hegedűs K.; Fülöp Á.; Wolfárt V.; Kadaikunnan S.; Khaled JM.; Alharbi NS.; Vágvölgyi C.; Galgóczy L. *In vitro* activity of calcium channel blockers in combination with conventional antifungal agents against clinically important filamentous fungi. *Acta Biol Hung*. **2017**, *68*, 334-344.

137. Bulatova NR.; Darwish RM. Effect of chemosensitizers on minimum inhibitory concentrations of FLC in *C. albicans*. *Med Princ Pract*. **2008**,*17*, 117-21.

138. Nattel S.; Singh BN. Evolution, mechanisms, and classification of antiarrhythmic drugs: focus on class III actions. *Am J Cardiol*. **1999**, *84(9A)*, 11R-19R.

139.   Kodama I.; Kamiya K.; Toyama J. Amiodarone: ionic and cellular mechanisms of action of the most promising class III agent. *Am J Cardiol*. **1999**, *84(9A)*, 20R-28R.

140.   Dorian P. Mechanisms of action of class III agents and their clinical relevance. *Europace*. **2000**, *1 Suppl C*, C6-9.

141.   Courchesne WE. Characterization of a novel, broad-based fungicidal activity for the antiarrhythmic drug amiodarone. *J Pharmacol Exp Ther*. **2002**, *300*, 195-9.

142.   Knorre DA.; Krivonosova TN.; Markova OV.; Severin FF. Amiodarone inhibits multiple drug resistance in yeast *Saccharomyces cerevisiae*. *Arch Microbiol*. **2009**, *191*, 675-9.

143.   Courchesne WE.; Tunc M.; Liao S. Amiodarone induces stress responses and calcium flux mediated by the cell wall in *Saccharomyces cerevisiae*. *Can J Microbiol*. **2009**, *55*, 288-303.

144.   Bagar T.; Benčina M. 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*. **2012**, *49*, 779-91.

145.   Afeltra J.; Vitale RG.; Mouton JW.; Verweij PE. Potent synergistic *in vitro* interaction between nonantimicrobial membrane-active compounds and ITR against clinical isolates of *Aspergillus fumigatus* resistant to ITR. *Antimicrob Agents Chemother*. **2004**, *48*, 1335-43.

146.   Gamarra S.; Rocha EM.; Zhang YQ.; Park S.; Rao R.; Perlin DS. Mechanism of the synergistic effect of amiodarone and FLC in *C. albicans*. *Antimicrob Agents Chemother*. **2010**, *54*, 1753-61.

147.   da 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. Synergistic effects of amiodarone and FLC on *C. tropicalis* resistant to FLC. *Antimicrob Agents Chemother*. **2013**, *57*, 1691-700.

148.   Gupta SS.; Ton VK.; Beaudry V.; Rulli S.; Cunningham K.; Rao R. Antifungal activity of amiodarone is mediated by disruption of calcium homeostasis. *J Biol Chem*. **2003**, *278*, 28831-9.

149.   Afeltra J.; Verweij PE. Antifungal activity of non-antifungal drugs. *Eur J Clin Microbiol Infect Dis*. **2003**, *22*, 397-407.

150.   Wood NC.; Nugent KM. Inhibitory effects of chlorpromazine on *Candida* species. *Antimicrob Agents Chemother*. **1985**, *27*, 692-4.

151.   Rossato L.; Loreto ÉS.; Zanette RA.; Chassot F.; Santurio JM.; Alves SH. *In vitro* synergistic effects of chlorpromazine and sertraline in combination with AmB against *C. neoformans* var. *grubii*. *Folia Microbiol (Praha)*. **2016**, *61*, 399-403.

152.   Sharma S.; Kaur H.; Khuller GK. Cell cycle effects of the phenothiazines: trifluoperazine and chlorpromazine in *C. albicans*. *FEMS Microbiol Lett*. **2001**, *199*, 185-90.

153.   Galgóczy L.; Bácsi A.; Homa M.; Virágh M.; Papp T.; Vágvölgyi C. *In vitro* antifungal activity of phenothiazines and their combination with AmB against different *Candida* species. *Mycoses*. **2011**, *54*, e737-43.

154.   Ben-Gigi G.; Polacheck I.; Eilam Y. *In vitro* synergistic activity of KET with trifluoperazine and with chlorpromazine against medically important yeasts. *Chemotherapy*. **1988**, *34*, 96-100.

155.   Wang Y.; Casadevall A. Susceptibility of melanized and nonmelanized *C. neoformans* to the melanin-binding compounds trifluoperazine and chloroquine. *Antimicrob Agents Chemother*. **1996**, *40*, 541-5.

156. Galgóczy L.; Papp T.; Kovács L.; Ordögh L.; Vágvölgyi C. *In vitro* activity of phenothiazines and their combinations with AmB against Zygomycetes causing rhinocerebral zygomycosis. *Med Mycol*. **2009**, *47*, 331-5.

157. Vitale RG.; Afeltra J.; Meis JF.; Verweij PE. Activity and post antifungal effect of chlorpromazine and trifluopherazine against *Aspergillus*, *Scedosporium* and zygomycetes. *Mycoses*. **2007**, *50*, 270-6.

158. Homa M.; Galgóczy L.; Tóth E.; Tóth L.; Papp T.; Chandrasekaran M.; Kadaikunnan S.; Alharbi NS.; Vágvölgyi C. *In vitro* antifungal activity of antipsychotic drugs and their combinations with conventional antifungals against *Scedosporium* and *Pseudallescheria* isolates. *Med Mycol*. **2015**, *53*, 890-5.

159. Krajewska-Kułak E.; Niczyporuk WW. Anticandidal activity of flunarizine. *Mater Med Pol*. **1993**, *25*,143-4.

160. Latendresse G.; Elmore C.; Deneris A. Selective serotonin reuptake inhibitors as first-line antidepressant therapy for perinatal depression. *J Midwifery Womens Health*. **2017**, *62*, 317-328.

161. Bandelow B.; Michaelis S.; Wedekind D. Treatment of anxiety disorders. *Dialogues Clin Neurosci*. **2017**, *19*, 93-107.

162. Oliveira AS.; Gaspar CA.; Palmeira-de-Oliveira R.; Martinez-de-Oliveira J.; Palmeira-de-Oliveira A. Anti-*Candida* activity of fluoxetine alone and combined with FLC: a synergistic action against FLC-resistant strains. *Antimicrob Agents Chemother*. **2014**, *58*, 4224-6.

163. Gu W.; Guo D.; Zhang L.; Xu D.; Sun S. The synergistic effect of azoles and fluoxetine against resistant *C. albicans* strains is attributed to attenuating fungal virulence. *Antimicrob Agents Chemother*. **2016**, *60*, 6179-88.

164. Naglik JR.; Challacombe SJ.; Hube B. *Candida albicans* secreted aspartyl proteinases in virulence and pathogenesis. *Microbiol Mol Biol Rev*. **2003**, *67*, 400-28.

165. Jiang L.; Zheng L.; Sun KA.; Zhou P.; Xu R.; Gu J.; Wei X. *In vitro* and *in vivo* evaluation of the antifungal activity of fluoxetine combined with antifungals against *C. albicans* biofilms and oral candidiasis. *Biofouling*. **2020**, *36*, 537-548.

166. Treviño-Rangel Rde J.; Villanueva-Lozano H.; Hernández-Rodríguez P.; Martínez-Reséndez MF.; García-Juárez J.; Rodríguez-Rocha H.; González GM. Activity of sertraline against *C. neoformans*: *in vitro* and *in vivo* assays. *Med Mycol*. **2016**, *54*, 280-6.

167. Treviño-Rangel RJ.; Villanueva-Lozano H.; Méndez-Galomo KS.; Solís-Villegas EM.; Becerril-García MA.; Montoya AM.; Robledo-Leal ER.; González GM. *In vivo* evaluation of the antifungal activity of sertraline against *Aspergillus fumigatus*. *J Antimicrob Chemother*. **2019**, *74*, 663-666.

168. Oliveira AS.; Martinez-de-Oliveira J.; Donders GGG.; Palmeira-de-Oliveira R.; Palmeira-de-Oliveira A. Anti-*Candida* activity of antidepressants sertraline and fluoxetine: effect upon pre-formed biofilms. *Med Microbiol Immunol*. **2018**, *207*, 195-200.

169. Paul S.; Mortimer RB.; Mitchell M. Sertraline demonstrates fungicidal activity *in vitro* for *Coccidioides immitis*. *Mycology*. **2016**, *7*, 99-101.

170. Cong L.; Liao Y.; Yang S.; Yang R. *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*. **2016**, *11*, e0167903.

171.   Gowri M.; Jayashree B.; Jeyakanthan J.; Girija EK. 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*. **2020**, *128*, 426-437.

172.   Fitzpatrick FA. Cyclooxygenase enzymes: regulation and function. *Curr Pharm Des*. **2004**, *10*, 577-88.

173.   Alem MA.; Douglas LJ. Effects of aspirin and other nonsteroidal anti-inflammatory drugs on biofilms and planktonic cells of *C. albicans*. *Antimicrob Agents Chemother*. **2004**, *48*, 41-7.

174.   Abdelmegeed E.; Shaaban MI. Cyclooxygenase inhibitors reduce biofilm formation and yeast-hypha conversion of FLC resistant *C. albicans*. *J Microbiol*. **2013**, *51*, 598-604.

175.   Ogundeji AO.; Pohl CH.; Sebolai OM. Repurposing of aspirin and ibuprofen as candidate anti-*Cryptococcus* drugs. *Antimicrob Agents Chemother*. **2016**, *60*, 4799-808.

176.   Yang S.; Liao Y.; Cong L.; Lu X.; Yang R. *In vitro* interactions between non-steroidal anti-inflammatory drugs and antifungal agents against planktonic and biofilm forms of *Trichosporon asahii*. *PLoS One*. **2016**, *11*, e0157047.

177.   Borba-Santos LP.; Nucci M.; Ferreira-Pereira A.; Rozental S. Anti-*Sporothrix* activity of ibuprofen combined with antifungal. *Braz J Microbiol*. **2020**.

178.   Alves LR.; Oliveira C.; Goldenberg S. Eukaryotic translation elongation factor-1 alpha is associated with a specific subset of mRNAs in *Trypanosoma cruzi*. *BMC Microbiol*. **2015**, *15*, 104.

179.   Nargesi S.; Rezaie S. 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*. **2018**, *47*, 770-772.

180.   Wu Y.; Totten M.; Memon W.; Ying C.; Zhang SX. *In vitro* antifungal susceptibility of the emerging multidrug-resistant pathogen *Candida auris* to miltefosine alone and in combination with amphotericin B. *Antimicrob Agents Chemother*. **2020**, *64*, e02063-19.

181.   Hai TP.; Van AD.; Ngan NTT.; Nhat LTH.; Lan NPH.; Vinh Chau NV.; Thwaites GE.; Krysan D.; Day JN. The combination of tamoxifen with amphotericin B, but not with fluconazole, has synergistic activity against the majority of clinical isolates of *Cryptococcus neoformans*. *Mycoses*. **2019**, *62*, 818-825.

182.   Yang J.; Gao L.; Yu P.; Kosgey JC.; Jia L.; Fang Y.; Xiong J.; Zhang F. *In vitro* synergy of azole antifungals and methotrexate against *Candida albicans*. *Life Sci*. **2019**, *235*, 116827.

183.   Kathwate GH.; Shinde RB.; Karuppayil SM. Antiepileptic drugs inhibit growth, dimorphism, and biofilm mode of growth in human pathogen *Candida albicans*. *Assay Drug Dev Technol*. **2015**, *13*, 307-12.

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.	[45]
Gentamicin	*Resistant-azole C. albicans*	>512	*G . mellonella*	FLC	(I) Suppresses overexpression of the efflux pump. (Ⅱ) Reduces phospholipase activity of resistant *C. albicans*.	[60]
Clarithromycin	*C. tropicalis*	-	-	AmB, ANI	-	[50]
	C. parapsilosis, C. glabrata, C. albicans	No effects		AmB		[49]
	Pythium insidiosum	0.25-8		-		[61]
Azithromycin	*Pythium insidiosum*	1-16	-	-	-	[61]
	Aspergillus spp.	No effects		AmB	Probably inhibits mitochondrial protein synthesis.	[62]
Norfloxacin	*C. albicans*	-	-	MIA	-	[46]
Levofloxacin	*C. albicans, A. fumigatus*	+	-	AmB, CAS	Probably inhibits fungal DNA replication by binding to fungal topoisomerase.	[63]
Gatifloxacin	*Candida spp.*	+	-	-	-	[64]
Moxifloxacin	*C. albicans*	+ [64]	-	Liposomal AmB [65], CAS [63]	Probably inhibits fungal DNA replication by binding to fungal topoisomerase.[63]	[63-65]
Ciprofloxacin	*C. albicans*	+	-	AmB	Probably inhibits fungal DNA replication by binding to *C. albicans* topoisomerase.	[63]
	A. fumigatus	+		AmB, CAS, ARC		
Trovafloxacin	*C. albicans*	No effects	Murine	FLC, AmB	-	[66]
	C. tropicalis, C. neoformans	No effects	-	FLC, AmB		
Tetracycline	*C. albicans*	320-2560 [51]	*G . mellonella*	AmB, FLC	-	[51,67]
Demeclocycline	*C. albicans*	640	-	AmB	-	[51]
Doxycycline	*C. parapsilosis, C. krusei, C. glabrata*	No effects	-	AmB	Probably inhibits protein synthesis.	[52]
	C. albicans	640-1280 [51]	*G . mellonella*	AmB, FLC, CAS	(I) Inhibits FLC-inducible efflux pump gene overexpression [70]. (Ⅱ) Disturbs calcium homeostasis [69,70].	[51,53,67-70]

					(III) Disturbs iron homeostasis [68].	
Minocycline	*C. albicans (fluconazole-resistance)*	256-512	-	AmB, FLC	Disturbs calcium homeostasis [71].	[51,71]
	A. fumigatus	0.125-4 [61]	*G. mellonella*	ITR, VRC, POS	Probably interferes with the balance of cellular electrolytes and loss of	[72]
	A. flavus, F. solani, F. oxysporum	0.125-4 [61]	-	ITR, VRC, POS	mitochondrial function.	
Tigecycline	*C. albicans*	2048	-	AmB, FLC, CAS	-	[54]
	Fusarium spp.	0.25-4		VRC, AmB	Inhibits the synthesis of protein [45].	[61]
Polymyxin B	*C. albicans*	-	-	AmB, KET, MIA	Probably alters cell membrane permeability.	[46]
	Fusarium spp.	4-16		VRC, AmB	Probably disturbs the synthesis of ergosterol.	[45]
	C. neoformans	8-256		FLC	Probably through binding anionic lipids on fungal membrane and destroys	[47]
	Rhizopus oryzae	32		-	membrane integrity.	
	A. fumigatus	28-56		-		
Rifampicin	*C. tropicalis*	-	-	AmB, ANI	-	[50]
	C. parapsilosis, C. glabrata, C. albicans, C. krusei	No effects		AmB	Probably disturbs RNA synthesis in the presence of AmB.	[52,61]
Linezolid	*Pythium insidiosum*	1-32	-	-	Inhibits protein synthesis.	[61]
	C. neoformans	> 64	-	AmB	-	[73]
	C. albican	> 512	*G . mellonella*	FLC, ITR, VRC	Probably inhibits mitochondrial protein synthesis and interferes with the induction of stress-response mitochondrial chaperones.	[74]

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.	[99-101]
	C. albicans	>10 [99]	Rat [100]	FLC, VRC, CAS,	Inhibits the expression of genes related to hyphal development, adhesion,	[96,99,100,102,103]
	Rhizopus spp., Lichtheimia spp., Mucor spp., Rhizomucor spp.	1-16	-	AmB ISA	biofilm formation and drug transporter in *C. albicans* [96].	[104]
Tacrolimus	*Trichosporon asahii*	> 64	-	AmB, CAS	Inhibits the activity of calcineurin pathway.	[105]
	Aspergillus spp.	0.25-16 [108]	Mice [107]	CAS		[105-107]
	Fusarium spp.	1-40	-	CAS		[109]
	C. albicans	No effects.	-	FLC, ITR, VRC		[102,110]
	C. dubliniensis	> 4	-	CAS, FLC, POS		[86]
	Rhizopus spp., Lichtheimia spp., Mucor spp., Rhizomucor spp.	1-8	-	ISA		[104]
Pimecrolimus	*Malassezia spp.*	16-64	-	-	-	[111]
Rapamycin	*C. albicans*	< 0.09- >100	-	-	Inhibits the TOR pathways via FKBP12-Rapa complex.	[112]
	C. neoformans	0.39- >100	-	-		[112]
	Mucor spp.	8	*G. mellonella* [113]	ISA		[104]
	Rhizopus spp., Lichtheimia spp., Rhizomucor spp.	8	-	ISA		[104]
	Phycomyces blakesleeanus	6.3-200	-	CAS, ISA		[113]
	Aspergillus spp.	16 [108]	Mice [107]	ISA [108]		[101,108]
Mycophenolic acid	*C. neoformans*	30	Nematode [81]	AmB	Disrupts *de novo* GTP biosynthesis.	[79]
	C. albicans	0.25	-	-		[80]
Mizoribine	*C. albicans*	-	-	-	Disrupt *de novo* GTP biosynthesis.	[80]
Dexamethasone	*Resistant-azole C. albicans*	No effects.	*G. mellonella*	FLC	Inhibits the drug efflux pump and reduce the activity of extracellular phospholipases.	[90]

Budesonide	*Resistant-azole C. albicans*	16- > 128	*G. mellonella*	FLC	(I) Inhibits the function of drug transporters.	[89]
					(II) Reduces the activity of extracellular phospholipases and the formation of biofilm.	
					(III) Promotes apoptosis by the accumulation of ROS.	
Hydrocortisone	*A. fumigatus*	-	-	ITR	-	[91]

Note: VRC, voriconazole; AmB, amphotericin B; FLC, fluconazole; ITR, itraconazole; POS, posaconazole; CAS, caspofungin; ISA, isavuconazole; -, no studies were mentioned in the corresponding references.
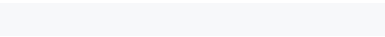
Table 3 Summary of statin drugs with antifungal activity

Statins	Fungus	*In vitro* (MIC: μg/mL)	*In vivo*	In combination (synergistic effects)	Relevant molecular mechanism	Ref.
Lovastatin	*Paecilomyces variotii*	64	-	-	-	[119]
	Rhizopus oryzae	128		-	-	
	C. albicans	50-64		FLC [119], ITR [120]	Inhibits ergosterol synthesis [120].	
	C. glabrata	128		FLC	-	
	A. fumigatus	25		FLC	-	
	Zygomycetes [121]	32-56		VRC	-	
Simvastatin	*C. glabrata*	16-32 [119]	-	-	(I) Inhibits ergosterol synthesis; (II) Causes the loss of mtDNA.	[121]
	C. albicans	8		MIA	-	[119]
	C. utilis	200		MIA	Inhibits ergosterol synthesis.	[123]
	Cryptococcus spp.	62.5-1000		AmB, ITR, FLC	Inhibits ergosterol synthesis.	[124]
	Saccharomyces cerevisiae	40		CTZ, ITR, MIA	Inhibits ergosterol synthesis.	[123]
	Paecilomyces variotii	8		-	-	[119]
	Rhizopus oryzae	64		-	-	[119]
	A. fumigatus	6.25		FLC	-	[119]
Pravastatin	*C. albican*	No effects.	Mice	FLC	Inhibits farnesol production.	[117]
Atorvastatin	*C. albicans*	16-256	*G. mellonella* [125]	MIA [119]	Inhibits ergosterol synthesis [125].	[114,119,125]
	C. glabrata	4-64	-	FLC [119]	-	[114,119,126]
	C. utilis	200	-	-	-	[124]
	C. krusei	8	-	-	-	[114]
	C. kefyr	4-16	-	-	-	[114]
	Cryptococcus gattii	≥ 256	Mice	FLC	(I) Inhibits ergosterol synthesis; (II) Induces the production of ROS.	[128]
	Saccharomyces cerevisiae	40	-	CTZ, ITR, MIA	-	[123]
	C. stellatoidea	16	-	-	-	[114]

	Rhizopus oryzae	**32**	-	**ITR, KET**	-	**[119]**
	Paecilomyces variotii	**32**	-	-	-	**[119]**
	Aspergillus flavus	**> 128**	-	**ITR**	-	**[119]**
	A. fumigatus	**64**	-	**ITR, FLC, MIA, KET**	**(I) Stimulates oxidative stress response;** **(II) Inhibits ergosterol synthesis [130].**	**[119]**
Fluvastatin	*C. albicans*	**25**	No effects in mice	**FLC**	-	**[119,126]**
	C. glabrata	**32-64**	-	-		**[119,126]**
	C. tropicalis	**128**	-	-		**[126]**
	C. dubliniensis	**16-512**	-	-		**[126]**
	Cryptococcus spp.	**64- >128**	-	**ITR, FLC**		**[128]**
	Paecilomyces variotii	**25**	-	-		**[119]**
	Rhizopus oryzae	**2-3.125**	-	**KET, ITR**		**[119]**
	A. fumigatus	**2**	-	-		**[119]**
	A. flavus	**128**	-	**KET, MIA, ITR**		**[119]**
Rosuvastatin	*C. albicans*	**8-128**	-	**MIA [119]**	-	**[126]**
	C. glabrata	**32-128**		-		**[119,126]**
	C. utilis	**200**		**MIA**		**[123]**
	Paecilomyces variotii	**32**		-		**[119]**
	Saccharomyces cerevisiae	**40**		**CTZ, ITR, MIA**		**[123]**
	Rhizopus oryzae	**>128**		**KET, ITR**		**[119]**
	A. fumigatus	**128**		**ITR**		**[119]**
	A. flavus	**>128**		-		**[119]**
Pitavastatin	*C. albicans, C. glabrata, C. auris*	**8**	*Caenorhabditis elegans*	**ITR, VRC, FLC**	-	**[129]**

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.

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.