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
treatin treatment of multicryptococcosis [29]. Additionally, due to their characteristic large molecular weight, low oral bioavailability, and limited absorption in the gastrointestinal tract, these drugs are only administered intravenously.

Azole resistance among Candida species such as C. auris and Aspergillus species, as well as echinocandin resistance in C. glabrata is an alarming problem [18]. In addition, other molds such as Scedosporium and Fusarium species have reduced susceptibility to clinically available antifungal drugs [18]. Although amphotericin B is recognized to have excellent antifungal activity, there are still fungi, such as Candida lusitaniae and Aspergillus terreus that show intrinsic resistance to amphotericin B [30]. Consequently, the development of new antifungals is needed to resolve this issue.

2. Drug repurposing strategy

With the changes in infection disease spectra and a clearer mechanism of disease, the strategy of drug repurposing to tap into new applications of existing drugs, requires innovative clinical in-depth investigation of pharmacological mechanisms. A large number of drugs with new indications have emerged. 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 disease that involves cardiovascular disease, stroke, and digestive tract cancers [31-34]. Vitamin D is widely used to regulate calcium and phosphate metabolism for bone health [35]. Recent studies have found that vitamin D deficiency is associated with an increased risk of cardiovascular disease, diabetes, hypercholesterolemia, and even the COVID-19 [36,37]. 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 [38-44]. 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).

3.1. Antibacterial drugs

The discovery of antibacterial drugs has been the greatest invention of medical science in reducing morbidity and mortality, and these drugs are mainly composed of tetracyclines (e.g., minocycline and doxycycline), aminoglycosides (e.g., gentamicin, neomycin, paromomycin, ribostamycin, and streptomycin), and quinolone polypeptides (e.g., moxifloxacin and gatifloxacin). 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. A number of reports have revealed that antibacterial drugs also 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 alone has 80 % activity and a 76 % synergistic effect with amphotericin B or...
voriconazole, respectively, and increases the permeability of the cell wall and cell membrane of fungi when combined with antifungal agents [45]. 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 [46]. Moreover, polymyxin B can integrate anionic lipids on the fungal membrane both alone and combined with fluconazole with a minimum concentration 8 μg/mL for Fusarium spp., C. neoformans, Rhizopus oryzae, and A. fumigatus, which destroys the membrane integrity [45,47].

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 [48]. 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 [48]. When combined with clarithromycin, the permeability barrier of the biofilm matrix was altered, which resulted in increased penetration of amphotericin B [49]. In addition, doxycycline, tigecycline, and rifampicin were also found to enhance the activity of amphotericin B to suppress biofilm formation [45, 49-54].

Thus, antibacterial drugs have potential antifungal value due to their good antifungal activity. However, human health is based on the balance of microbiota [55,56]. Although antibacterial drugs have been approved for the treatment of invasive fungal infections, many problems still need to be considered. For instance, antibiotic treatment will reduce the composition of colonized microbiota [57]. 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 [57]. 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 [58,59]. In addition, the pharmacokinetics of antibiotics with antifungal activity in vivo also require further investigation.

3.2. 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; tacrolimus, FK506; and pimecrolimus), target of rapamycin inhibitors (e.g., rapamycin), antimetabolic agents (e.g., mycophenolic acid, MPA; mizoribine, MZP), and glucocorticoids (e.g., hydrocortisone, budesonide, and dexamethasone). Initially, rapamycin was found to be an antifungal agent and inhibited yeasts including C. albicans, dermatophytes, Microsporum gypseum, and Trichophyton granulosum [75]. Rapamycin, probably acting on the recombinant FK506 binding protein (FKBP) complex, showed activity on clinical isolates of Candida compared with candidicidin, nystatin, and amphotericin B in an in vitro investigation [76]. 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 [77]. 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 [78]. 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 [79-81]. 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 [82, 83].

Calcineurin, a conserved serine-threonine specific phosphatase, consists of a catalytic subunit and a regulatory subunit [84, 85]. It is one of the important mediators in calcium signals and is involved in hyphal/mycelium formation in C. neoformans and A. fumigatus [86]. Clinical experience has suggested that calcineurin inhibitors (cyclosporin A and FK506) can decrease the mortality of invasive Aspergillosis by forming protein-drug complexes [87, 88]. Glucocorticoids, such as hydrocortisone, budesonide, and dexamethasone, are immunosuppressants with antifungal activity [89-91]. However, the antifungal activity of glucocorticoids remains controversial. For instance, an investigation found that hydrocortisone enhanced the growth of Aspergillus spp. [92]. 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 [93]. Moreover, an in vivo investigation also found that glucocorticoids increased fungal burden in the gastrointestinal tract in rats [94], and enhanced the frequency of fungal translocation in mice [95]. 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 [96, 97]. 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 [98]. 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.

3.3. Statins

Statins are firstly known as lipid-lowering and cholesterol-lowering drugs as they inhibit HMG-CoA reductase (an essential enzyme in cholesterol biosynthesis) [114], 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* [115]. 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* [116], and in contrast, no synergy was found between pravastatin and fluconazole *in vitro* in another investigation [117]. In addition, a study even reported that pravastatin did not inhibit the growth of *Candida spp.* [118]. The reason for this may be due to differences in fungi strains, and different methodology. These contradictory findings require clarification in further investigations.

3.4. Antiarrhythmic drugs

Antiarrhythmic drugs, which are used in the prevention and treatment of tachycardia, bradyarrhythmia, or arrhythmia, include sodium channel antagonists, β-receptor blockers, potassium channel blockers (PCRs), and calcium channel blockers (CCBs). Trails 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 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 [131,132]. In addition, verapamil enhances the antifungal activity of tunicamycin or fluconazole against *C. albicans* during biofilm formation and pre-formed biofilms [133]. In *A. fumigatus*, the drug efflux pump was blocked and ergosterol content was decreased following treatment with verapamil and itraconazole simultaneously [134]. Other CCBs, such as diltiazem, nicardipine, and nifedipine, have shown antifungal activity against *C. albicans*, *C. glabrata*, Ascomycetes and Mucoralean fungi, either alone or in combination with antifungals [135-137]. Amiodarone is known to block potassium, sodium and calcium channels, and is commonly used to treat and prevent tachyarrhythmia [138-140]. 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* [141-147]. In addition, amiodarone displayed potent fungicidal effects at low dose combined with fluconazole and miconazole [148]. Hence, calcium channels may be potential targets in the therapy of fungal-related infections.

3.5. Antipsychotic drugs

Antipsychotic drugs include benzamides, butyrophenones, dibenzoazepine, phenothiazines, and thioxanthenes. 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 [149], which may explain the antifungal action of
phenothiazines [150,151]. Chlorpromazine and trifluoperazine are representative phenothiazines. Both block the central dopamine D2 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]. Flunarazine is a difluorinated derivative of piperazine as well as a potent CCB. It has the same structure as phenothiazines. Flunarazine 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)
NSAIDs, act mainly by inhibiting the activity of cyclooxygenase to reduce the production of prostaglandins (PGs), thus have antipyretic, analgesic, anti-inflammatory, and other functions [172]. 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* [173,174]. In addition, most of these drugs had synergistic or additive (ketorolac) activity with fluconazole against *C. albicans* [174]. 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 [175]. In addition, aspirin and ibuprofen combined with fluconazole, caspofungin, and amphotericin B have effects on fungi [175,176]. 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 [177]. Diclofenac sodium can down-regulate the expression of *Ef-1* gene, which is involved in cellular RNA transport, cell cycle, and apoptosis [178], thus resulting in a reduction in the formation of *A. fumigatus* filaments [179].

4. Conclusion

In this review, we summarized the antifungal effects of a number of non-antifungal agents. In addition, some antitumor agents such as miltefosine [180], tamoxifen [181], methotrexate, [182] and antiepileptic drugs [183] have also 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 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, as well as collect more clinical data to evaluate the antifungal effectiveness of these agents.

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# 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                        | (1) Suppresses overexpression of the efflux pump.                                           | [60] |
|                  |                                 |                       |         |                                      | (II) Reduces phospholipase activity of resistant C. albicans.                                |      |
| 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. [63-65]      |      |
| Ciprofloxacin    | C. albicans                     | +                     | -       | AmB                                 | Probably inhibits fungal DNA replication by binding to C. albicans topoisomerase. [63]    |      |
|                  | A. fumigatus                    | +                     | -       | AmB, CAS, ARC                        | -                                                                                           | [63] |
| Trovafoxacin     | C. albicans                     | No effects            | Murine  | FLC, AmB                             | -                                                                                           | [66] |
|                  | C. tropicalis, C. neoformans    | No effects            | -       | FLC, AmB                             | -                                                                                           | [66] |
| Tetracycline     | C. albicans                     | 320-2560 [51]         | G, mellonella | AmB, FLC                           | -                                                                                           | [51,67] |
| Demechocycline   | C. albicans                     | 640                   | -       | AmB                                 | -                                                                                           | [51] |
| Doxycycline      | C. parapsilosis, C. krusei, C. glabrata | No effects           | -       | AmB                                 | (1) Inhibits FLC-inducible efflux pump gene overexpression [70].                              | [52] |
|                  | C. albicans                     | 640-1280 [51]         | G, mellonella | AmB, FLC, CAS | (1) ) Inhibits FLC-inducible efflux pump gene overexpression [70].                             | [51,53,67-70] |
|                  |                                 |                       |         |                                      | (II) Disturbs calcium homeostasis [69,70].                                                   |      |
(III) Disturbs iron homeostasis [68].

| Antibiotic | Fungi | MIC (μg/mL) | Susceptibility | Effect | Reference |
|------------|-------|-------------|----------------|--------|-----------|
| **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 mitochondrial function. | [72] |
| | *A. flavus, F. solani, F. oxysporum* | 0.125-4 [61] | - | ITR, VRC, POS | - | |
| **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 membrane integrity. | [47] |
| | *Rhizopus oryzae* | 32 | - | - | - | |
| | *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.
| Immunosuppressants | Fungus | In vitro (MIC: μg/mL) | In vivo (synergistic effects) | Relevant molecular mechanism | Ref. |
|--------------------|--------|-----------------------|-----------------------------|-----------------------------|------|
| **Cyclosporine**   |        |                       |                             |                             |      |
| Aspergillus spp.   |        | 1-25                  | -                           | CAS, ISA                    |      |
| C. albicans        |        | >10 [99]              | Rat [100]                   | FLC, VRC, CAS, AmB          | [99-101] |
| Rhizopus spp., Lichtheimia spp., Mucor spp., Rhizomucor spp. | 1-16 | - | AmB | Inhibits the calcineurin pathways. | [96,99,100,102,103] |
| Tacrolimus         |        | > 64                  | -                           | AmB, CAS                    | [105] |
| Trichosporon asahii |       |                       |                             |                             |      |
| Aspergillus spp.   |        | 0.25-16 [108]         | Mice [107]                  | CAS                         | [109] |
| Fusarium spp.      |        | 1-40                  | -                           | CAS                         | [102,110] |
| C. albicans        |        | No effects.           | -                           | FLC, ITR, VRC              | [86] |
| C. dubliniensis    |        | > 4                   | -                           | CAS, FLC, POS              | [104] |
| Rhizopus spp., Lichtheimia spp., Mucor spp., Rhizomucor spp. | 1-8 | - | ISA | Inhibits the activity of calcineurin pathway. | [105-107] |
| Pimecrolimus       | Malassezia spp. | 16-64                 | -                           |                             | [111] |
| Rapamycin          | C. albicans | < 0.09- >100          | -                           | -                           | [111] |
|                    | C. neoformans | 0.39- >100         | -                           | -                           | [111] |
|                    | Mucor spp. | 8                     | G. mellonella [113]         | ISA                         | [104] |
|                    | Rhizopus spp., Lichtheimia spp., Rhizomucor spp. | 8 | - | ISA | Inhibits the TOR pathways via FKBP12-Rapa complex. | [112] |
|                    | 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                         | [79] |
|                    | C. albicans | 0.25                  | -                           | -                           | [80] |
| Mizoribine         | C. albicans | -                     | -                           | -                           | [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.
| Statins   | Fungus                        | In vitro (MIC: μg/mL) | In vivo | In combination (synergistic effects) | Relevant molecular mechanism | Ref.               |
|-----------|-------------------------------|-----------------------|---------|--------------------------------------|-----------------------------|--------------------|
| Lovastatin | Paecilomyces variotii         | 64                    | -       | -                                    | (I) Inhibits ergosterol synthesis; (II) Causes the loss of mtDNA. | [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]           | -       | -                                    |                             | [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]              |
| Yeast Family          | Minimal Inhibitory Concentration (MIC) | Anti-Fungal Activity                          | Notes                                                                 |
|-----------------------|----------------------------------------|-----------------------------------------------|----------------------------------------------------------------------|
| *Rhizopus oryzae*     | 32                                     | -                                             | ITR, KET                                                              |
| *Paecilomyces variotii* | 32                                     | -                                             | -                                                                    |
| *Aspergillus flavus*  | >128                                   | -                                             | ITR                                                                  |
| *A. fumigatus*        | 64                                     | -                                             | ITR, FLC, MIA, KET (I) Stimulates oxidative stress response; (II) Inhibits ergosterol synthesis [130]. |
| **Fluvasatin**        |                                        |                                               |                                                                       |
| C. *albicans*         | 25                                     | No effects in mice                            | FLC                                                                  |
| C. *glaabrata*        | 32-64                                  | -                                             | -                                                                    |
| C. *tropicalis*       | 128                                    | -                                             | -                                                                    |
| C. *dublilensis*      | 16-512                                 | -                                             | -                                                                    |
| Cryptococcus spp.     | 64-128                                 | +                                             | ITR, FLC                                                             |
| *Paecilomyces variotii* | 25                                     | -                                             | -                                                                    |
| *Rhizopus oryzae*     | 2-3.125                                | -                                             | KET, ITR                                                             |
| *A. fumigatus*        | 2                                      | -                                             | -                                                                    |
| *A. flavus*           | 128                                    | -                                             | KET, MIA, ITR                                                        |
| **Rosuvastatin**      |                                        |                                               |                                                                       |
| C. *albicans*         | 8-128                                  | -                                             | MIA [119]                                                            |
| C. *glaabrata*        | 32-128                                 | -                                             | -                                                                    |
| C. *utilis*           | 200                                    | -                                             | MIA                                                                  |
| *Paecilomyces variotii* | 32                                     | -                                             | -                                                                    |
| Saccharomyces cerevisiae | 40                                    | -                                             | CTZ, ITR, MIA                                                        |
| *Rhizopus oryzae*     | >128                                   | -                                             | KET, ITR                                                             |
| *A. fumigatus*        | 128                                    | -                                             | ITR                                                                  |
| *A. flavus*           | >128                                   | -                                             | -                                                                    |
| **Pitavastatin**      |                                        |                                               |                                                                       |
| C. *albicans, C. glaabrata, C. auris* | 8                                      | Caenorhabditis elegans                        | ITR, VRC, FLC                                                         |

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.