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EDITORIAL

# Statins as antifungal agents

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## Abstract

Fungal infections are increasing and their treatment is difficult, because the most widely used antifungal drugs are relatively toxic and have serious side effects. Therefore, interest has focused on safely applicable and clinically introduced non-antifungal drugs, which have potent antifungal activity. Statins were originally used as cholesterol lowering agents in human therapy, but recent studies demonstrated their *in vitro* antifungal activity against yeasts and filamentous fungi. This indicated their potential application, alone or in combination with other drugs, in the treatment of such diseases. Their effective concentrations are higher than their maximum achievable serum levels; therefore, the application of statins for the treatment of invasive fungal infections is only possible in combination with antifungal agents. These synergistic combinations establish a basis for a new safely applicable therapy. This review focuses on the antifungal activity of statins alone and in combination with antifungal and non-antifungal drugs, and their possible application in clinical therapy.



**Key words:** Statins; Antifungal activity; Drug interaction

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## INTRODUCTION

The incidence of invasive fungal infections (IFIs) is increasing because of the growing number of immunocompromised hosts and the occurrence of antibiotic resistant strains. The major risk factors for these diseases are the administration of broad-spectrum antibiotics, corticosteroids and cytotoxic agents, intravenous catheters, invasive medical procedures, human immunodeficiency virus infection, poorly controlled diabetes mellitus, hematological malignancy, solid organ or bone marrow transplantation, steroid use, metabolic acidosis, deferoxamine therapy, and severe and prolonged neutropenia[1,2]. Treatment of IFIs is difficult, because the most widely applied antifungal drugs [e.g. amphotericin B (AMB)] for treatment of such disease are relatively toxic and have serious side effects. Therefore, there is a substantial interest in clinically introduced non-antifungal drugs that have potent antifungal activity and/or can act synergistically with antifungal agents to allow a decrease in their therapeutic concentrations. Such compounds would form the basis of a less toxic therapy[3]. Statins are interesting from this respect, as they have effective antifungal potential against both yeast and filamentous fungi; furthermore, they can be combined with clinically used antifungal agents.

## STATINS

### *History of statins*

Statins were discovered as cholesterol lowering drugs in the 1970s, and are the most widely prescribed medications worldwide[4].

Statins are metabolites of microorganisms (mevastatin, MEV; lovastatin, LOV; simvastatin, SIM and pravasatin, PRA) or fully synthetic compounds (atorvastatin, ATO; cerivastatin, CER; fluvastatin, FLV; pitavastatin, PIT; and rosuvastatin, ROS). The natural statins are substituted hexahydronaphthalene lactones. The first described statin, MEV, was isolated as a secondary metabolite of a *Penicillium citrinum* strain. Subsequently, further intensive fungal screenings for similar compounds revealed that a strain of both *Aspergillus terreus* and *Monascus ruber* produce a more efficient statin, LOV[5]. SIM is a post-methylated derivative of LOV[6], and PRA was isolated from the fermentation broth of an Actinobacteria species, *Nocardia autotrophica*[7].

After successful clinical trials of the natural statins, pharmaceutical companies introduced more effective and safer fully synthetic statins. The structures of synthetic statins are dissimilar and are different from the natural statins, except for the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)-like moiety, which is responsible for HMG-CoA reductase inhibition, which, indirectly, results in their cholesterol lowering effects[8]. FLV was the first fully synthetic statin, followed by ATO, CER, PIT, and ROS[5]. CER has been withdrawn from the market because of its serious adverse effect (fatal rhabdomyolysis)[9].

Statins were observed to have unexpected antifungal effects and their potential application in the treatment of fungal diseases has been intensively studied.

### Mechanism of statins' effects

Statins are competitive inhibitors of HMG-CoA reductase, which catalyses the conversion of HMG-CoA to mevalonate, a rate-limiting step in the isoprenoid biosynthetic pathway, which is involved in the synthesis of cholesterol in humans and ergosterol in fungi[10]. Statins compete with the natural substrate for the enzyme's active site, preventing the formation of a functional enzyme structure with reversible binding[11].

Thus, the effects of statins are connected with the inhibition of the synthesis of important isoprenoids, e.g. farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are important lipid attachments for the γ subunit of heterotrimeric G-proteins[12], guanosine triphosphate-binding protein Ras, and Ras-like proteins (Rho, Rab, Rac, Ral, or Rap)[12-14]. Thus, statins act as inhibitors of some G-protein actions and Ras or Ras-like signaling, which affect several important bioprocesses[15].

Figure 1 summarizes the metabolic pathway of sterols and the impact of statins in their biosynthesis[16,17].

## ANTIFUNGAL ACTIVITY OF STATINS

The *in vitro* antifungal activity of statins against yeasts and filamentous fungal isolates has been frequently reported, and all the studies propose their potential application, alone or in combination, in clinical therapy. The different fungi are not equally sensitive to statins *in vitro*, e.g. SIM exhibits the strongest antifungal activity against yeasts compared to filamentous fungi, whereas the reverse is true for FLV[18]. The natural statins (e.g. SIM and LOV) mainly effect their antifungal activity in their active metabolite forms (hydrolysis of the lactone ring at pH 10), and they proved to be less effective as pro-drugs[18,19]. Generally, the synthetic statins are more effective than the natural ones[18,19].

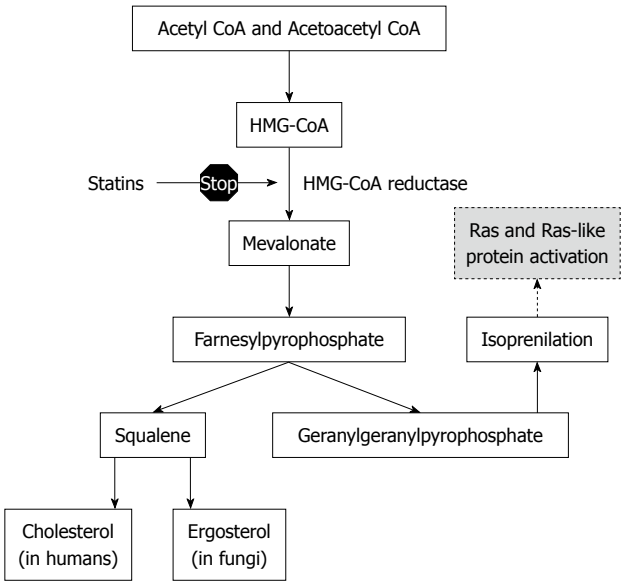


**Figure 1 Metabolic pathway of sterols and the impact of statins in their bioprocess[16,17].**

### Antifungal activity of statins against yeasts

Statins exhibit fungicidal or fungistatic effects against yeasts in a dose dependent-manner. Data concerning the antifungal activity of various statins against yeasts are available for *Candida albicans* (*C. albicans*), *Candida glabrata* (*C. glabrata*), *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, *Cryptococcus neoformans* (*C. neoformans*), and *Saccharomyces cerevisiae*[18,20-29]. These studies demonstrated that the various statins exhibit different antifungal effects against yeasts. SIM displayed the strongest antifungal activity, followed by FLV, ATO, ROS, and LOV. PRA proved to be completely ineffective against them. The antifungal activity of FLV is dependent on the pH of the medium[27]. Table 1 shows the available minimal inhibitory concentration (MIC) values of the investigated statins against yeast species.

The growth inhibition effect of statins on yeast cells is related to the decreasing ergosterol level, which occurs because of the inactivation of HMG-CoA reductase inactivation by statins in the isoprenoid biosynthetic pathway[16]. Ergosterol is a main constituent of the lipid layer of fungal plasma membranes, and the antifungal effect might arise from decreased membrane fluidity in the yeast cells[24]. This assumption is confirmed by the observation that supplementation with ergosterol or cholesterol reduced the antifungal effect of statins[20,25,26], and that *C. albicans* transformed from the yeast cell form to the

**Table 1 Determined minimal inhibitory concentration values (μg/mL) of different statins against *Candida* species**

| Statin/species | ATO | FLV | LOV | PRA | ROS | SIM | Ref. |
|---|---|---|---|---|---|---|---|
| *Candida albicans* | 128 | 25-128 | 5-64 | > 128 | 128 | 8 | [18,21,22,29] |
| *Candida glabrata* | 32 | 64-> 128 | 128 | > 128 | 128 | 16-32 | [18,21,29] |
| *Candida parapsilosis* | ND | 64-128 | ND | ND | ND | ND | [21] |
| *Candida tropicalis* | ND | 64-128 | ND | ND | ND | ND | [21] |
| *Cryptococcus neoformans* | ND | 16-32 | ND | ND | ND | ND | [21] |

ATO: Atorvastatin; FLV: Fluvastatin; LOV: Lovastatin; PRA: Pravastatin; ROS: Rosuvastatin; SIM: Simvastatin; ND: Not determined.

**Table 2 Determined minimal inhibitory concentration values (μg/mL) of different statins against filamentous fungal species**

| Statin/Species | ATO | FLV | LOV | PRA | ROS | SIM | Ref. |
|---|---|---|---|---|---|---|---|
| Zygomycetes | | | | | | | |
| *Absidia corymbifera* | 96[1] | > 25-3.6 | > 96 | > 96 | 33[1] | 96[1] | [19,35] |
| *Absidia glauca* | ND | 6.25 | ND | ND | ND | ND | [35] |
| *Cunninghamella bertholletiae* | ND | ND | 32-40 | ND | ND | ND | [33] |
| *Micromucor ramanniana* | ND | > 25 | ND | ND | ND | ND | [35] |
| *Mortierella wolfii* | > 128 | ND | > 128 | ND | > 128 | > 128 | [34] |
| *Mucor circinelloides* | ND | ND | 5-40 | ND | ND | ND | [33] |
| *Mucor circinelloides f. lusitanicus* | ND | > 25 | ND | ND | ND | ND | [35] |
| *Mucor hiemalis* | ND | > 25 | ND | ND | ND | ND | [35] |
| *Mucor mucedo* | ND | 6.25 | ND | ND | ND | ND | [35] |
| *Mucor racemosus* | ND | 25 | ND | ND | ND | ND | [35] |
| *Mycotypha africana* | 8 | ND | > 128 | ND | 8 | > 128 | [34] |
| *Paecilomyces variotii* | 32 | 25 | 64 | > 128 | 32 | 8 | [29] |
| *Rhizomucor mieheii* | > 96 | 6.25 | 64-> 128 | > 96 | 33[1] | > 96 | [19,32,35] |
| *Rhizomucor pusillus* | > 96 | 3.125 | 1-3.6[1] | > 96 | 11[1] | 33[1] | [19,32,35] |
| *Rhizopus homothallicus* | ND | ND | 40-56 | ND | ND | ND | [33] |
| *Rhizopus microsporus var. oligosporus* | > 96 | 96[1] | > 96 | > 96 | > 96 | > 96 | [19] |
| *Rhizopus oryzae* | 32-96[1] | 2-11[1] | 32-128 | > 128 | > 128 | 64-> 96[1] | [18,19,29,33,35] |
| *Rhizopus schipperae* | ND | > 25 | ND | ND | ND | ND | [35] |
| *Rhizopus stolonifer* | 64 | | > 128 | | 64 | > 128 | [34] |
| *Saksenaea vasiformis* | ND | > 25 | ND | ND | ND | ND | [35] |
| *Syncephalastrum racemosum* | 32-> 96 | 33[1] | 16-> 96 | > 96 | 32-> 96 | 8-> 96 | [19,34,35] |
| Ascomycetes | | | | | | | |
| *Aspergillus flavus* | > 128 | 128 | > 128 | > 128 | > 128 | > 128 | [18,29] |
| *Aspergillus fumigatus* | 64-> 256 | 2 | 25 | > 128 | 128-> 256 | 6.25 | [18,29,37] |
| *Aspergillus spp.* | ND | ND | 16-256 | ND | ND | 4-256 | [36] |
| *Paecilomyces variotii* | 32 | 25 | 64 | > 128 | 32 | 8 | [18] |
| Heterokontophyta | | | | | | | |
| *Pythium insidiosum* | ND | 16-64 | ND | ND | ND | ND | [38] |

[1]$MIC_{90}$ value. ATO: Atorvastatin; FLV: Fluvastatin; LOV: Lovastatin; PRA: Pravastatin; ROS: Rosuvastatin; SIM: Simvastatin; ND: Not determined.

pseudomycelial form upon exposure to LOV[24]. It is also proposed that antimicrobial activity based on the loss of mitochondrial DNA, and thus the respiratory function of the cell, occurs in the presence of statins[16]. Indirectly, the antifungal effect of statins might come from their negative influence on the cell signaling by the inhibition of the synthesis of lipid attachments for the γ subunit of heterotrimeric G-proteins[15], and on the cell proliferation and differentiation through inhibition of the synthesis of important isoprenoids[30]. LOV does not cause apoptotic cell death in yeasts compared to filamentous fungi[24,31].

### *Antifungal activity of statins against filamentous fungi*

The inhibition activity of statins on the growth of filamentous fungi was revealed in the cases of several zygo-[18,19,28,31-35] and ascomycetous fungal species[18,25,28,29,36,37]. Only one article reports the antifungal activity of FLV against a Heterokontophyta fungal species, *Pythium insidiosum*[38]. In contrast to its activity against yeasts, FLV displayed the strongest antifungal activity, followed by ROS, SIM, LOV, and ATO. PRA also proved to be ineffective against them. Table 2 summarizes the determined MIC values of statins against different filamentous fungal species.

Beyond to the harmful effects on membrane fluidity and the synthesis of important isoprenoids for cell signaling and vital processes (such as cell proliferation and differentiation), and protein prenylation[16], statins induce apoptosis-like cell death in filamentous fungi[15,30,31]. The molecular mechanisms underlying the different levels of fungal resistance to statins are unknown. It is hypothesized that the resistance is connected with the different copy numbers of the HMG-CoA reductase gene (hmgR) in the case of filamentous species. This assumption is supported by the observation of Lukács *et al*[39]. In their

study, heterologous expression of the *Rhizomucor miehei hmg*R gene in *Mucor circinelloide* lowered its sensitivity to statins compared to the untransformed strain. Furthermore, supplementation of sterols to the medium reduces the antifungal activity of statins, as in the case of yeasts[25].

## ANTIFUNGAL ACTIVITY OF STATINS IN DRUG COMBINATIONS

Statins are not applicable as single antifungal agents for the treatment of IFI because their MICs are much higher (about 1 order of magnitude) than their maximum achievable concentrations in human serum[11,40-45]. All the same, they should be promising agents in clinical practice because they can act additively or synergistically with antifungal agents, allowing substantial decreases in their therapeutic concentrations and their side effects[45]. Such combinations would be advantageous as the basis of a less toxic antifungal therapy[3].

### *Combination with antifungal agents*

Statins can interact synergistically with azole antifungal agents against yeasts and can reduce their growth significantly. Fluconazole (FCZ) with LOV, and FCZ or itraconazole (ITZ) with FLV, interact synergistically on the growth of *Candida* species[21,22]; however, interaction was not demonstrated between PRA or FLV and FCZ[23]. FLV acted additively with AMB, FCZ, and ITZ against *C. albicans* and *C. neoformans*[21]. Both synergistic and additive effects were observed on the growth reduction of *C. albicans* and *C. glabrata* when primycin (PN), a non-polyene macrolide lactone antibiotic complex, was combined with FLV, LOV, or SIM[18]. Additive interactions were observed between AMB and ATO and ROS, and between nystatin (NYS) and FLV, LOV, ROS, and SIM in the case of *C. albicans* and *C. glabrata*[28]. A recent comprehensive study, where the interaction was investigated between four different azole compounds (FCZ; ITZ; ketoconazole, KTZ; and miconazole; MCZ) and six different statins (ATO, FLV, LOV, PRA, ROS, and SIM), revealed synergistic and additive interaction between these compounds against *C. albicans* and *C. glabrata*[29]. Table 3 summarizes these interactions.

Synergistic and additive interactions were revealed between statins and antifungal agents in the case of zygomycetous fungal species[18,19,28,29,33]. Significant *in vitro* synergy between statins and azole antifungal agents was demonstrated against several zygomycete fungi, though voriconazole itself was ineffective[29,33]. Remarkable antifungal effects were observed on the growth of *Rhizopus oryze* when PN was combined with statins in concentrations that could not inhibit the fungal growth alone[18]. In the case of this species, AMB and NYS also interacted additively with different statins[28]. *In vitro*, FLV and ROS acted synergistically and additively with AMB in inhibiting the growth of fungi belonging to Zygomycetes over their clinically available concentration ranges in human serum[19]. After *in vivo* tests, these concentration combinations may represent a promising basis for combined therapy in the treatment of invasive zygomycosis.

Synergistic and/or additive interaction of AMB, caspofungin, VCZ, PN with FLV on the growth reduction of *Aspergillus fumigatus* was demonstrated[28,37]. AMB acted additively with ATO and FLV against *Aspergillus flavus*[28]. Synergistic interaction was observed between PN and FLV, LOV and SIM, and an additive interaction was observed between AMB and ATO or SIM in the case of *Paecilomyces variotii*[18,28]. Additive and synergistic interactions were revealed between statins and azoles against *A. flavus*, *A. fumigatus*, and *Paecilomyces variotii*[29].

Terbinafine acted antagonistically in combination with FLV against *P. insidiosum*. Reduced antifungal activity was observed for their combination compared to when they were applied alone[38].

### *Combination with other drugs*

Drug interactions were revealed between statins and non-antifungal drugs, which have a secondary antifungal activity. An antifungal peptide secreted by *Penicillium chrsyogenum* (*Penicillium chrsyogenum* antifungal protein; PAF) and a hexasulfonated naphtylurea, suramin (originally applied as an agent for treatment of parasitic infections) can decrease the growth of zygomyceteous fungal species in the presence of different statins[34,35]. The activities of the statin-PAF combinations on the different strains varied, and depended on the activities of the components applied separately. When a strain was resistant to one of the components, significant interactions could not be detected. On the other hand, when a strain was sensitive to both types of antifungal agents, synergistic or additive interactions were detected[34]. Interactions were not detected between FLV and suramin if the investigated strain proved to be insensitive to both compounds, but synergistic and additive interactions could be observed if the fungus was sensitive to FLV and insensitive to suramin. Antagonistic interaction was observed if the fungus was sensitive to both drugs[35].

These results are summarized in Table 4.

## STATINS AS ANTIFUNGAL AGENTS IN CLINICAL THERAPY

A number of studies detail the beneficial effects of statins in transplant or non-transplant recipients with sepsis or infection[16]. One theory of the possible clinical therapy for invasive mould infection (IMI) among immunocompromised patients was created based on the observation that this disease in patients with diabetes mellitus appears to be decreasing over recent years because of the more frequent use of statins in these patients[46]. This hypothesis is well supported by the above-mentioned *in vitro* susceptibility and drug interaction studies; however, a recent retrospective case-control study suggested that, despite evidence of *in vitro* activity, statins may not decrease risk of IMI[47].

In consequence, because the *in vitro* observed MICs

**Table 3 Revealed *in vitro* interactions between statins and clinically used antifungal agents against different fungi**

| Species | Antifungal agent | Statin | Interaction | Ref. |
|---|---|---|---|---|
| Yeasts | | | | |
| *Candida albicans* | AMB | ATO, FLV | ADD | [28,21] |
| | FCZ, ITZ, KTZ | ATO | ADD | [29] |
| | FCZ, ITZ | FLV | ADD, SYN, NI | [21,23,29] |
| | | LOV | SYN, ADD | [22,29] |
| | FCZ, ITZ, KTZ, MCZ | PRA | NI | [23,29] |
| | FCZ,KTZ | ROS | ADD | [29] |
| | FCZ, ITZ, KTZ | SIM | ADD | [29] |
| | ITZ, KTZ, MCZ | FLV, LOV | ADD | [29] |
| | ITZ,MCZ | ROS | SYN, ADD | [29] |
| | MCZ | ATO,SIM | SYN, ADD | [29] |
| | PN, NYS | FLV, LOV, SIM | ADD | [18,28] |
| *Candida glabrata* | AMB | ATO, ROS | ADD | [18] |
| | FCZ | ATO | SYN, ADD | [29] |
| | FCZ, ITZ | FLV | ADD, NI | [21,29] |
| | FCZ | LOV | SYN, ADD | [29] |
| | FCZ, ITZ | PRA | NI | [29] |
| | FCZ, ITZ, KTZ, MCZ | ROS, SIM | ADD | [29] |
| | ITZ, KTZ, MCZ | ATO, FLV, ROS | ADD | [29] |
| | KTZ, MCZ | PRA | ADD | [29] |
| | PN | ATO, FLV | ADD | [18] |
| | | LOV, SIM | ADD, SYN | [18] |
| | NYS | LOV, ROS | ADD | [28] |
| *Candida parapsilosis* | FCZ, ITZ | FLV | ADD, SYN | [21] |
| *Candida tropicalis* | FCZ | FLV | SYN | [21] |
| | ITZ | FLV | ADD, SYN | [21] |
| *Cryptococcus neoformans* | FCZ, ITZ | FLV | ADD, SYN | [21] |
| | AMB | FLV | ADD | [21] |
| Filamentous fungi-Zygomycetes | | | | |
| *Absidia corymbifera* | AMB | ROS | ADD, SYN | [19] |
| *Cunninghamella bertholletiae* | VCZ | LOV | SYN | [33] |
| *Mucor circinelloides* | VCZ | LOV | SYN | [33] |
| *Rhizomucor mieheii* | AMB | FLV, ROS | ADD, SYN | [19] |
| *Rhizopus homothallicus* | VCZ | LOV | SYN | [33] |
| *Rhizopus microsporus var. oligosporus* | AMB | FLV, ROS | ADD, SYN | [19] |
| *Rhizopus oryzae* | AMB | FLV, ROS | ADD, SYN | [19,28] |
| | | ATO, SIM | ADD | [28] |
| | FCZ | FLV | NI | [29] |
| | FCZ, ITZ, MCZ | LOV | ADD | [29] |
| | ITZ, KTZ | ATO, FLV, ROS | SYN, ADD | [29] |
| | ITZ, KTZ, MCZ | PRA | NI | [29] |
| | ITZ, KTZ | SIM | NI | [29] |
| | KTZ | LOV | NI | [29] |
| | MCZ | ATO | NI | [29] |
| | | FLV, ROS, SIM | ADD | [29] |
| | NYS | ATO, FLV, LOV | ADD | [28] |
| | PN | ATO | ADD | [18] |
| | | LOV, ROS | SYN | [18] |
| | VCZ | LOV | SYN | [33] |
| *Syncephalastrum racemosum* | AMB | FLV, ROS | ADD, SYN | [28] |
| Filamentous fungi-Ascomycetes | | | | |
| *Aspergillus flavus* | AMB, PN | FLV | ADD, SYN | [18,28] |
| | ITZ | ATO | SYN | [29] |
| | ITZ, KTZ, MCZ | FLV | SYN, ADD | [29] |
| | ITZ | LOV | ADD | [29] |
| | ITZ, KTZ | PRA | NI | [29] |
| | ITZ | ROS | ADD | [29] |
| | ITZ, MCZ | SIM | ADD | [29] |
| | KTZ | ATO, ROS | SYN, ADD | [29] |
| | | SIM | NI | [29] |
| | MCZ | ATO, LOV, ROS | NI | [29] |
| | | PRA | ADD | [29] |
| *Aspergillus fumigatus* | AMB | ATO, FLV | ADD, SYN | [28,37] |
| | CFG, VCZ | FLV | SYN | [37] |
| | FCZ, ITZ | ATO | SYN | [29] |
| | FCZ, ITZ, MCZ | FLV | ADD | [29] |
| | FCZ | LOV | SYN | [29] |

| | | | | |
|---|---|---|---|---|
| | FCZ | SIM | SYN, ADD | [29] |
| | ITZ, KTZ, MCZ | LOV, SIM | ADD | [29] |
| | | PRA | NI | [29] |
| | ITZ | ROS | SYN, ADD | [29] |
| | KTZ, MCZ | ATO | SYN, ADD | [29] |
| | KTZ | FLV | SYN, ADD | [29] |
| | KTZ, MCZ | ROS | ADD | [29] |
| *Paecilomyces variotii* | AMB | ATO,SIM | ADD | [28] |
| | PN | FLV, LOV, SIM | SYN | [18] |
| Filamentous fungi-Heterokontophyta | | | | |
| *Pythium insidiosum* | TBF | FLV | ANT | [37] |

ADD: Additive interaction; AMB: Amphotericin B; ANT: Antagonism; ATO: Atorvastatin; CFG: Capofungin; FCZ: Fluconazole; FLV: Fluvastatin; ITZ: Itraconazole; KTZ: Ketoconazole; LOV: Lovastatin; MCZ: Miconazole; NI: No interaction; NYS: Nystatin; PN: Primycin; PRA: Pravastatin; ROS: Rosuvastatin; SIM: Simvastatin; SYN: Synergistic interaction; TBF: Terbinafine; VCZ: Voriconazole.

**Table 4 Revealed *in vitro* interactions between statins and non-antifungal drugs against zygomycetous fungi**

| Species | Non-antifungal drug | Statin | Interaction | Ref. |
|---|---|---|---|---|
| Zygomycetes | | | | |
| *Absidia corymbifera* | SUR | FLV | SYN | [35] |
| *Absidia glauca* | SUR | FLV | ANT | [35] |
| *Micromucor ramanniana* | SUR | FLV | SYN | [35] |
| *Mucor circinelloides f. lusitanicus* | SUR | FLV | ADD, SYN | [35] |
| *Mucor racemosus* | SUR | FLV | ANT | [35] |
| *Mycotypha africana* | PAF | ATO, SIM | ADD | [34] |
| | | LOV, ROS | ADD, SYN | [34] |
| *Rhizomucor mieheii* | SUR | FLV | ANT | [35] |
| *Rhizomucor pusillus* | SUR | FLV | ANT | [35] |
| *Rhizopus oryzae* | SUR | FLV | ADD, SYN | [35] |
| *Rhizopus schipperae* | SUR | FLV | ADD, SYN | [35] |
| *Saksanaea vasiformis* | SUR | FLV | ADD, SYN | [35] |
| *Syncephalastrum racemosum* | PAF | ATO | ADD, SYN | [34] |
| | | ROS, SIM | SYN | [34] |
| | SUR | FLV | ADD, SYN | [35] |

ADD: Additive interaction; ANT: Antagonism; ATO: Atorvastatin; FLV: Fluvastatin; LOV: Lovastatin; PAF: *Penicillium chrysogenum* antifungal protein; ROS: Rosuvastatin; SIM: Simvastatin; SUR: Suramin; SYN: Synergistic interaction.

of statins are higher than their concentrations achievable in human serum, their potential application to prevent or treat IMIs is only possible in combination with antifungal agents[45]. In clinical practice, the administration of statins together with antifungals, which are metabolized by different cytochrome P450 (CYP450) isoenzymes in the liver, suggests that the drug interactions with the CYP system and the serious adverse effects (e.g. myopathy) are avoidable[45].

## FUTURE PROSPECTIVES

The number of antifungal agents available for treatment of IFIs is limited, and their use has been restricted because of their toxicity or unfavorable pharmacokinetic profiles[3]. Hence, research interest has focused on safe, non-antifungal drugs that are used in clinical practice and have antifungal activity.

The observed *in vitro* antifungal activities of statins and their combinations with clinically antifungal agents would create new therapies for the treatment of IFI, without serious side effects. However, there are some factors in their combined application that require increased attention in immunocompromised hosts. As a consequence of the pleiotropic beneficial effects of statins beyond their lipid lowering attributes, there is a decreased risk of chronic renal failure and an improved endothelial dysfunction)[16]. Importantly, the administration of statins together with antifungals that are predominantly metabolized by the same CYP450 isoenzymes in the liver is contraindicated, because such drug interactions with the CYP system may cause serious adverse effects[45].

Further studies, for example, *in vivo* animal model experiments, are needed to evaluate the practical efficiency and possible triggered side effects of statin-antifungal drug combinations.

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