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AIM AND SCOPE

World Journal of Clinical Infectious Diseases (World J Clin Infect Dis, WJCID, online ISSN 2220-3176, DOI: 10.5495) is a bimonthly peer-reviewed, online, open-access, journal supported by an editorial board consisting of 106 experts in infectious diseases from 35 countries.

WJCID will focus on a broad spectrum of topics on infectious diseases that will cover epidemiology, immune-pathogenesis, genetic factors, host susceptibility to infection, vector control, novel approaches of treatment, molecular diagnostic and vaccines. It will provide a common stage to share the visions, new approaches, most advanced techniques, and to discuss research problems that will help everyone working in the field of various infections to exchange their views and to improve public health. WJCID will also focus on broad range of infections like opportunistic infections, zoonotic infections, tropical and neglected tropical diseases, emerging infections, etc. and following topics related to these issues: (1) Causative agents discussing various pathogens; (2) Vectors and Mode of transmission; (3) Host-pathogen interaction and immune-pathogenesis of the disease; (4) Epidemiology of the infection and vector control strategies; (5) Genetic factors covering both host and pathogen; (6) Molecular diagnostic techniques vaccines; and (7) Recent advances in cell tissue culture, lab techniques, etc. Various other related fields like medical microbiology, pharmacology of herbs, bioinformatics, etc. will be included.

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Statins as antifungal agents

László Galgóczy, Ildikó Nyilasi, Tamás Papp, Csaba Vágvölgyi

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 (mevatatin, MEV; lovastatin, LOV; simvastatin, SIM and pravastatin, PRA) or fully synthetic compounds (lovastatin, ATO; cerivastatin, CER; fluvastatin, FLV; pitavastatin, PIT; and rosuvastatin, ROS). The natural statins are substituted hexahydro-naphthalene lactones. The first described statin, MEV, was isolated as a secondary metabolite of a Penicilium 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[7]. 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 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[20]. 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[21]. 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

---

**Figure 1** Metabolic pathway of sterols and the impact of statins in their bioprocess[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[10]. The natural statins (e.g. SIM and LOV) mainly affect 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].
suppressed pseudomycelial form upon exposure to LOV\textsuperscript{[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\textsuperscript{[10]}. 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 \( \gamma \) subunit of heterotrimeric G-proteins\textsuperscript{[15]} and on the cell proliferation and differentiation through inhibition of the synthesis of important isoprenoids\textsuperscript{[10]}. LOV does not cause apoptotic cell death in yeasts compared to filamentous fungi\textsuperscript{[10,11].}

**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-

\textsuperscript{[18,19,28,30]}

and ascomycetous fungal species\textsuperscript{[24,25,28,29,36,37]}. Only one article reports the antifungal activity of FLV against a Heterokon-

tophysa fungal species, *Pythium insidiosum*\textsuperscript{[39]}. In contrast to its activity against yeasts, FLV displayed the strongest antifungal activity, followed by ROS, SIM, LOV, and ATO. ATO 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\textsuperscript{[14]}, statins induce apoptosis-like cell death in filamentous fungi\textsuperscript{[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 \textit{et al}\textsuperscript{[39]}. In their

### Table 1

<table>
<thead>
<tr>
<th>Statin/species</th>
<th>ATO</th>
<th>FLV</th>
<th>LOV</th>
<th>PRA</th>
<th>ROS</th>
<th>SIM</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida albicans</em></td>
<td>128</td>
<td>25-128</td>
<td>5-64</td>
<td>&gt; 128</td>
<td>128</td>
<td>8</td>
<td>[18,21,22,29]</td>
</tr>
<tr>
<td><em>Candida glabrata</em></td>
<td>32</td>
<td>64-128</td>
<td>128</td>
<td>&gt; 128</td>
<td>128</td>
<td>8</td>
<td>[18,21,29]</td>
</tr>
<tr>
<td><em>Candida parapsilosis</em></td>
<td>ND</td>
<td>64-128</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[21]</td>
</tr>
<tr>
<td><em>Candida tropicalis</em></td>
<td>ND</td>
<td>64-128</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[21]</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>ND</td>
<td>16-32</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[21]</td>
</tr>
</tbody>
</table>

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

### Table 2

<table>
<thead>
<tr>
<th>Statin/Species</th>
<th>ATO</th>
<th>FLV</th>
<th>LOV</th>
<th>PRA</th>
<th>ROS</th>
<th>SIM</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zygomycetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Abidia cornubiéra</em></td>
<td>96</td>
<td>&gt; 25-3.6</td>
<td>&gt; 96</td>
<td>&gt; 96</td>
<td>33</td>
<td>96</td>
<td>[19,35]</td>
</tr>
<tr>
<td><em>Abidia glauca</em></td>
<td>ND</td>
<td>6.25</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[35]</td>
</tr>
<tr>
<td><em>Cunninghamella bertholletiae</em></td>
<td>ND</td>
<td>ND</td>
<td>32-40</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[33]</td>
</tr>
<tr>
<td><em>Micromucor ramosaniana</em></td>
<td>ND</td>
<td>&gt; 25</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[35]</td>
</tr>
<tr>
<td><em>Mortierella alpina</em></td>
<td>&gt; 128</td>
<td>ND</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
<td>[34]</td>
</tr>
<tr>
<td><em>Mucor circinelloides</em></td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>5-40</td>
<td>ND</td>
<td>ND</td>
<td>[33]</td>
</tr>
<tr>
<td><em>Mucor circinelloides f. leucosporus</em></td>
<td>ND</td>
<td>&gt; 25</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[35]</td>
</tr>
<tr>
<td><em>Mucor hiemalis</em></td>
<td>ND</td>
<td>&gt; 25</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[35]</td>
</tr>
<tr>
<td><em>Mucor muscoides</em></td>
<td>ND</td>
<td>6.25</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[35]</td>
</tr>
<tr>
<td><em>Mucor racemosus</em></td>
<td>ND</td>
<td>25</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[35]</td>
</tr>
<tr>
<td><em>Mycobacteria africana</em></td>
<td>8</td>
<td>ND</td>
<td>&gt; 128</td>
<td>ND</td>
<td>8</td>
<td>&gt; 128</td>
<td>[34]</td>
</tr>
<tr>
<td><em>Paecilomyces variotii</em></td>
<td>32</td>
<td>25</td>
<td>64</td>
<td>&gt; 128</td>
<td>32</td>
<td>8</td>
<td>[29]</td>
</tr>
<tr>
<td><em>Rutrosporum miehei</em></td>
<td>&gt; 96</td>
<td>6.25</td>
<td>64-128</td>
<td>&gt; 96</td>
<td>33</td>
<td>&gt; 96</td>
<td>[19,32,35]</td>
</tr>
<tr>
<td><em>Rutrosporum puellus</em></td>
<td>&gt; 96</td>
<td>3.125</td>
<td>1-3.6</td>
<td>&gt; 96</td>
<td>11</td>
<td>33</td>
<td>[19,32,35]</td>
</tr>
<tr>
<td><em>Rutrosporum homothallicus</em></td>
<td>ND</td>
<td>ND</td>
<td>40-56</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[33]</td>
</tr>
<tr>
<td><em>Rutrosporum microsporum var. oligonorum</em></td>
<td>&gt; 96</td>
<td>96</td>
<td>&gt; 96</td>
<td>&gt; 96</td>
<td>&gt; 96</td>
<td>&gt; 96</td>
<td>[19]</td>
</tr>
<tr>
<td><em>Rutrosporum oryzae</em></td>
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<td>2-11</td>
<td>32-128</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
<td>[18,19,29,33,35]</td>
</tr>
<tr>
<td><em>Rutrosporum schirpeae</em></td>
<td>ND</td>
<td>&gt; 25</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[35]</td>
</tr>
<tr>
<td><em>Sakataea vossii</em></td>
<td>ND</td>
<td>&gt; 25</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[35]</td>
</tr>
<tr>
<td><em>Saccaromyces cerevisiae</em></td>
<td>32</td>
<td>&gt; 96</td>
<td>33</td>
<td>16-96</td>
<td>&gt; 96</td>
<td>32-96</td>
<td>&gt; 8-96</td>
</tr>
<tr>
<td><em>Aspergillus flavus</em></td>
<td>&gt; 128</td>
<td>128</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
<td>[18,29]</td>
</tr>
<tr>
<td><em>Aspergillus fumigatus</em></td>
<td>64-256</td>
<td>2</td>
<td>25</td>
<td>&gt; 128</td>
<td>128-256</td>
<td>6.25</td>
<td>[18,29,37]</td>
</tr>
<tr>
<td><em>Aspergillus niger</em></td>
<td>ND</td>
<td>ND</td>
<td>16-256</td>
<td>ND</td>
<td>ND</td>
<td>4-256</td>
<td>[56]</td>
</tr>
<tr>
<td><em>Paracoccidioides variotii</em></td>
<td>32</td>
<td>25</td>
<td>64</td>
<td>&gt; 128</td>
<td>32</td>
<td>8</td>
<td>[18]</td>
</tr>
<tr>
<td><em>Heterokonothypa</em></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pythium insidiosum</em></td>
<td>ND</td>
<td>16-64</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>[38]</td>
</tr>
</tbody>
</table>

1MICs value. ATO: Atorvastatin; FLV: Fluvastatin; LOV: Lovastatin; PRA: Pravastatin; ROS: Rosuvastatin; SIM: Simvastatin; ND: Not determined.
study, heterologous expression of the *Rhzomucor miehei* hmgR gene in *Mucor circinelloides* 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.

**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. 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. Such combinations would be advantageous as the basis of a less toxic antifungal therapy.

**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; however, interaction was not demonstrated for PRA or FLV and FCZ. FLV acted additively with AMB, FCZ, and ITZ against *C. albicans* and *C. neoformans*. 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. Additive interactions were observed between AMB and ATO and ROS, and between nystatin (NYS) and FLV, LOV, POS, and SIM in the case of *C. albicans* and *C. glabrata*. A recent comprehensive study, where the interaction was investigated between four differentazole compounds (FCZ, ITZ, ketoconazole, KTG, 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*. Table 3 summarizes these interactions.

Synergistic and additive interactions were revealed between statins and antifungal agents in the case of zygomycetous fungal species. Significant *in vitro* synergy between statins and azole antifungal agents was demonstrated against several zygomycete fungi, though voriconazole itself was ineffective. Remarkable antifungal effects were observed on the growth of *Rhizopus oryzae* when PN was combined with statins in concentrations that could not inhibit the fungal growth alone. In the case of this species, AMB and NYS also interacted additively with different statins. In *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. After *in vitro* 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. AMB acted additively with ATO and FLV against *Aspergillus flavus*. 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*. Additive and synergistic interactions were revealed between statins and azoles against *A. flavus*, *A. fumigatus*, and *Paecilomyces variotii*.

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

**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 chrysogenum* (*Penicillium chrysogenum* antifungal protein; PAF) and a hexasulfonated naphthylurea, suramin (originally applied as an agent for treatment of parasitic infections) can decrease the growth of zygomycetaceous fungal species in the presence of different statins. 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. 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.

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. 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. 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.

In consequence, because the *in vitro* observed MICs...
### Table 3  Revealed in vitro interactions between statins and clinically used antifungal agents against different fungi

<table>
<thead>
<tr>
<th>Species</th>
<th>Antifungal agent</th>
<th>Statin</th>
<th>Interaction</th>
<th>Ref.</th>
</tr>
</thead>
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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. In clinical practice, the administration of statins together with antifungals, which are metabolized by different CYP450 isoenzymes in the liver, suggests that the drug interactions with the CYP system and the serious adverse effects (e.g. myopathy) are avoidable.

**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. 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. 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.

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.

**REFERENCES**

nini F. New insights into the pharmacodynamic and pharmaco-
metabolic properties of statins. Pharmacol Ther 1999; 84: 413-428
Pharmacol Toxicol 2005; 45: 89-118
13 Liao JK. Isoprenoids as mediators of the biological effects of
14 Ghittori R, Patrussi L, Pirozzi K, Pellegrini M, Lazzerini
PE, Capecchi PL, Pasini FL, Baldari CT. Simvastatin inhibits
T-cell activation by selectively impairing the function of Ras
superfamily GTPases. FASEB J 2005; 19: 605-607
15 Cordle A, Koenigsknecht-Talbo J, Wilkinson B, Limpert A,
Landreth G. Mechanisms of statin-mediated inhibition of
16 Sun HY, Singh N. Antimicrobial and immunomodulatory
attributes of statins: relevance in solid-organ transplant re-
17 Lefebvre M, Alishawa K, Dupont B. L'activité antifongique
18 Nyilasi I, Kocsobé S, Pesthi M, Lukács G, Papp T, Vágvölgyi C.
In vitro interactions between primycin and different statins
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sterol levels and on activity of azoles in Saccharomyces cere
19 Galgóczy L, Lukács G, Nyilasi I, Papp T, Vágvölgyi C. Antifun-
gal activity of statins and their interaction with amphi-
tericin B against clinically important Zygomycetes. Antimicrob
Agents Chemother 2006; 50: 96-103
20 Galgóczy L, Papp T, Lukács G, Leiter E, Pócsi I, Vágvölgyi C.
Interactions between statins and Penicillium chrysoge-
num antifungal protein (PAF) to inhibit the germination of
sporangiospores of different sensitive Zygomycetes. FEMS
21 Galgóczy L, Papp T, Vágvölgyi C. In vitro interaction be-
tween suramin and fluconazole against clinically important
22 Qiao J, Kontoyiannis DP. L'activité antifongique
23 Cavalheiro AS, Zanette RA, Spader TB, Lovato L, Azevedo
MI, Botton S, Alves SH, Santurio JM. In vitro activity of terbi-
nofungin associated to amphotericin B, fluconazil, rifampicin,
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 Vet Microbiol 2009; 137: 408-411
24 Natesan SK, Chandrasekar PH, Alangaden GJ, Manavathu
EK. Fluconazil potentiates the activity of caspofungin against
Aspergillus fumigatus in vitro. Diagn Microbiol Infect Dis
2008; 60: 369-373
25 Cavaleiro AS, Zanette RA, Spader TB, Lovato L, Azevedo
MI, Botton S, Alves SH, Santurio JM. In vitro activity of terbi-
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 Vet Microbiol 2009; 137: 408-411
26 Lókás G, Papp T, Nyilasi I, Pócsi I, Vágvölgyi C. Cloning of the Rhizomucor miehei 3-hydroxy-
3-methylglutaryl-coenzyme A reductase gene and its het-
rerologous expression in Mucor circinnelloides. Antonie Van
Leeuwenhoek 2009; 95: 55-64
27 Kajinami K, Takekoshi N, Saito Y. Pitavastatin: efficacy and
safety profiles of a novel synthetic HMG-CoA reductase in-
28 Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on
clinical pharmacokinetics and drug interactions. Circulation
2004; 109: 1135-1157
29 Corsini A, Bellosta S, Davidson MH. Pharmacokinetic in-
teractions between statins and fibrates. Am J Cardiol 2005; 96:
44K-49K; discussion 34K-35K
30 Schachter M. Chemical, pharmacokinetic and pharmacody-
namic properties of statins: an update. Fundam Clin Pharma-
col 2005; 19: 117-125
31 Buemi M, Flocchini F, Nostro L, Campo S, Caccamo C, Sturia-
le A, Aloisi C, Giacobbe MS, Frisina R. Simvastatin reduces the
death process in the fungus Mucor racemosus. Fungal Genet
Biol 1998; 25: 119-133
32 Mihád T, Hirayama S, Nakamura Y. Cholesterol-indepen-
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33 Roze LV, Linz JE. Lovastatin triggers an apoptosis-like cell
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34 Sun HY, Singh N. Antimicrobial and immunomodulatory
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35 Lefebvre M, Alishawa K, Dupont B. L’activité antifongique
36 Nyilasi I, Kocsobé S, Galgóczy L, Papp T, Pesthi M, Vágvöl-
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37 Nyilasi I, Kocsobé S, Krizsák K, Galgóczy L, Pesthi M, Papp T,
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fungi. FEMS Microbiol Lett 2010; 307: 175-184
38 Miya T, Hirayama S, Nakamura Y. Cholesterol-indepen-
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39 Roze LV, Linz JE. Lovastatin triggers an apoptosis-like cell
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40 S- Editor Wang JL. L- Editor Stewart G. E- Editor Zheng XM

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