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ORIGINAL ARTICLE/ARTICLE ORIGINAL

Luliconazole, an alternative antifungal agent against *Aspergillus terreus*

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Summary *Aspergillus terreus* is the fourth leading cause of invasive and non-invasive aspergillosis and one of the causative agents of morbidity and mortality among immunocompromised and high-risk patients. *A. terreus* appears to have increased as a cause of opportunistic fungal infections from superficial to serious invasive infections. Although, invasive aspergillosis is often treated empirically with amphotericin B, most *A. terreus* isolates are resistant both in vivo and in vitro to some antifungal drugs. In this study, we aimed to evaluate antifungals susceptibility profiles of the different strains of *A. terreus* against amphotericin B, caspofungin, fluconazole, voriconazole, posaconazole and luliconazole. Forty *A. terreus* strains originating from environmental sources (air and soil) were identified using by macroscopic and microscopic features. Six antifungals including, amphotericin B, caspofungin, fluconazole, voriconazole, posaconazole and luliconazole were applied for susceptibility tests. Our results show that tested isolates had different susceptibility to antifungals. The lowest MIC_{GM} related to luliconazole (0.00236 μg/ml), followed by posaconazole (0.18621 μg/ml), voriconazole (0.22925 μg/ml), caspofungin (0.86 μg/ml), fluconazole (8 μg/ml) and amphotericin B (11.12 μg/ml). This study demonstrated that luliconazole had an excellent in vitro activity against all tested isolates of *A. terreus*, with MIC_{GM} 0.00236 μg/mL than other tested antifungals. As a result, luliconazole could be a possible alternative antifungal for the treatment of aspergillosis due to *A. terreus*.

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Introduction

Aspergillus terreus is an opportunistic fungus that has been described as one of the causative agent of aspergillosis in the recent years [1]. For example, endocarditis [2], spondylodiscitis [3], pulmonary aspergillosis, endophthalmitis [4,5], onychomycosis [6], otomycosis [7], osteomyelitis, aspergillosis of bone and joint [8], mycotic aneurysm [9], mycocarditis [10] and keratitis [11]. *A. terreus* is classified as a hyaline mold with widely existence in throughout the world in soil, air and vegetable materials. Furthermore, tropical and sub-tropical areas are presenting favorable conditions for growing *A. terreus* [6,11].

Invasive aspergillosis is a life-threatening infection with high mortality in immunocompromised patients. The mortality rate of disease is high, about 85% and around 50% if treated with antifungals [12]. *A. terreus* causes of a range of diseases including, superficial, subcutaneous and systemic infections as well as allergic reactions [2,11,13]. Invasive infections by this species make up about 4% of all invasive aspergillosis and the mortality rates are higher than other species of *Aspergillus* [1].

Amphotericin B, voriconazole, and posaconazole are classical antifungal drugs, which commonly use in the treatment of aspergillosis [14]. Usually, in clinic, voriconazole is prescribed as the first-line antifungal therapy for invasive aspergillosis, however aspergillosis infections with *A. terreus* have been failed in 52.9% of cases in comparison to 65.3% for other antifungal drugs [1]. Common causative agents aspergillosis are relatively sensitive to amphotericin B, however, intrinsically, resistance to amphotericin B is seen in *A. terreus* [15]. Resistance to amphotericin is due to differences in quality and quantity of membrane lipid compositions (especially ergosterol) [16]. In contrast, a recent study showed that resistance to amphotericin is not associated with the cell membrane ergosterol [17]. Posaconazole was discussed as an antifungal choice for prophylaxis in high-risk patients [18]. However, fluconazole is as one of the safest antifungals for the therapy of fungal infections, but because of increased resistance in fungi it has limited its use [19]. Furthermore, it has been demonstrated that *Aspergillus* species have intrinsic resistance to fluconazole [20–22].

Recently, caspofungin (Cancidas) was used for the treatment of invasive aspergillosis and candidiasis especially in AIDs patients [17,23–25]. Cancidas is comparable in efficacy and safety with other antifungals for invasive mycosis as well as less toxic than amphotericin B [17,25]. Luliconazole ($C_{14}H_9Cl_2N_3S_2$) is an imidazole antifungal drug that approved for the treatment of cutaneous mycosis in Japan from 2005 as 1% cream (Luzu) [26]. Drug is highly effective against dermatophytes and *Candida* species in vitro [26,27]. On the other hand, luliconazole has excellent tolerability and no systemic side effects were reported when used as topical preparation [28,29]. However, in a few cases skin erythema was reported [30]. Although, luliconazole recently was more used for the treatment of dermatophytosis, researches show that it is also effective against *Aspergillus* species [31,32]. Luliconazole is newly under evaluation by researchers for *Aspergillus* species and some studies have shown that luliconazole has significantly effect on *A. fumigatus* [32].

In the present study, we aimed to evaluate antifungals susceptibility profile of different environmental strains of *A. terreus* against six antifungal drugs including, amphotericin B, caspofungin, fluconazole, voriconazole, posaconazole and luliconazole.

Materials and methods

Collocation of *A. terreus* strains and identification

A. terreus strains were captured from air and soil samples. All samples were inoculated on Sabouraud dextrose agar (SDA) (Merck, Germany) and incubated at ambient temperature for at least one week. All suspected *A. terreus* isolates were detected by morphological and microscopy features. Colonies of *A. terreus* on SDA were velvety, cinnamon to brown with radial folds. The microscopic morphology of *A. terreus* including, long conidiophores, globose vesicles, compact, columnar and biseriate phialides with globose to ellipsoidal conidia. Moreover, the laterally attached aleurioconidia (3–5 μm in diameter) to vegetative mycelium are the main identical characteristic of *A. terreus* (Fig. 1) [33,34].

Antifungals stock preparation

A stock solution of caspofungin (Sigma–Aldrich, Germany) 1.25 mg/ml, amphotericin B (Sigma–Aldrich, Germany) 32 mg/ml, fluconazole (Serva, USA) 32 mg/ml, luliconazole (APIChem Technology, China) 80 mg/ml, posaconazole (Sigma–Aldrich, Germany) 1.75 mg/ml and voriconazole

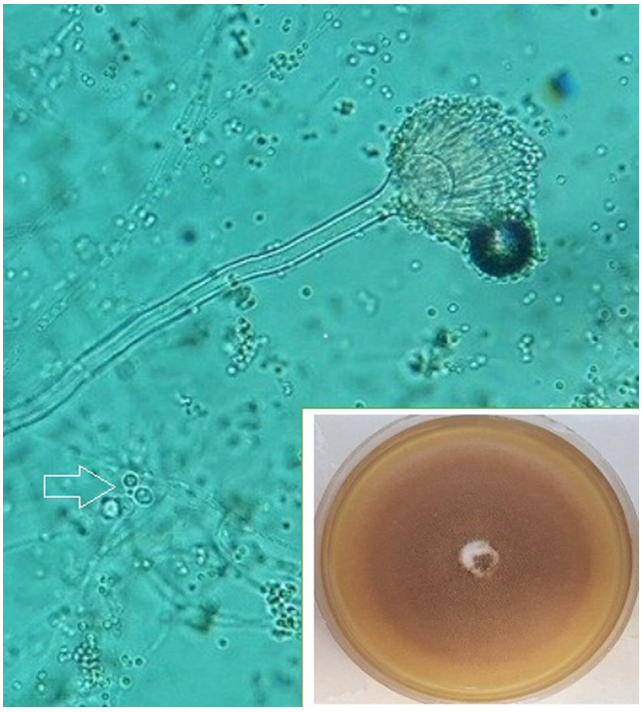

Figure 1 Colony and microscopy morphology of *Aspergillus terreus* (arrow shows aleurioconidia).

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