Research on antifungal activity of a new azole compound, YZJT-1903

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Objective: Fluconazole is widely used to treat invasive fungal infections, but the fluconazole resistance of pathogenic fungi undermines its antifungal efficacy. Although voriconazole has a good anti-A. fumigatus activity, it is not a first-line drug for treating infections caused by Candida and Cryptococcus species. To meet the demand for new azoles, in our previous studies, we identified a new azole compound, YZJT-1903 (Fig. 1a), and found that YZJT-1903 has a longer in vivo half-life (>10 days in rat) and a wider therapeutic window than voriconazole, indicating that YZJT-1903 is a promising azole compound to treat invasive fungal infections. In this study, we further investigated antifungal activity of YZJT-1903 compared with fluconazole and voriconazole.

Methods: We investigated the antifungal spectrum of YZJT-1903 and minimum inhibitory concentration (MIC) and accumulative antifungal percentage of YZJT-1903 against various pathogenic fungi using microbroth dilution method. We quantitatively analyzed the inhibitory effect of YZJT-1903 on fungal growth by the Time-Growth Curve assay. Minimal Preventive Concentration (MPC) was carried out to verify the antifungal potential of YZJT-1903. Sterols of plasma membrane were extracted and the composition was analyzed through Gas Chromatograph-Mass Spectrometer (GC-MS) to verify the classical action mechanism of azoles.

Results: Our MIC assay results demonstrated that YZJT-1903 has a broad antifungal spectrum and significantly inhibit the growth of A. fumigatus, Cryptococcus neoformans, Cryptococcus gattii, and Candida species (such as Candida albicans, C. tropicalis, C. parapsilosis, C. glabrata, C. pseudotropicalis, and C. auris) (Fig. 1a). We found that the antifungal activity of YZJT-1903 is equivalent to that of voriconazole, but superior to that of fluconazole (Fig. 1a). Accumulative antifungal percentage can directly reflect the relationship quantitatively among YZJT-1903, fluconazole, and voriconazole due to the curve of YZJT-1903 has no significance with voriconazole (Fig. 1b). YZJT-1903 (0.25 μg/ml) has similar inhibitory effect to voriconazole (0.25 μg/ml) on the growth of C. albicans and C. neoformans, but has the best inhibitory effect on C. auris [compared with voriconazole (0.25 μg/ml) and fluconazole (0.25 μg/ml)] (Fig. 1c). MPC of YZJT-1903 is C. neoformans is as low as 0.25 μg/ml which means YZJT-1903 at low concentration can already prevent the drug-resistant strain from reproducing, therefore, avoid the occurrence of resistance to Cryptococcus spp. (Fig. 1d). Restriction of sterols showed that the fungal cell-bound with YZJT-1903 at 0.063 μg/ml have completely no detectable ergosterol which is similar to the group of fluconazole at 0.4 μg/ml, and the group of voriconazole at 0.031 μg/ml (Fig. 2). This result gives a hint that maybe the property of YZJT-1903 is more similar to voriconazole which may mate with the structure of these two compounds. We found that fungal ergosterol 100 μg are ergosterol-consumed and concomitant decreases the antifungal activity of YZJT-1903, indicating that YZJT-1903 has an antifungal activity by inhibiting the synthesis of ergosterol.

Conclusion: Our study demonstrates that YZJT-1903 has a potent antifungal activity, which will contribute to addressing devastating global invasive fungal infections caused by Candida and Cryptococcus species.
Candidemia in a tertiary care hospital: epidemiology, speciation and antifungal susceptibility pattern

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Objective: The incidence of bloodstream fungal infection is on the rise and Candida species remains responsible for the majority of the cases. Candida auris is frequently associated with a high rate of mortality and morbidity. The purpose of this study was to characterize Candidemia, its epidemiology, species distribution, and antifungal susceptibility pattern in a tertiary care hospital.

Methods and Material: Candida species isolated from the blood culture of 51 patients in a tertiary care hospital during the period from 2016 to 2021 were included in the study. The growth on SDA was confirmed by Gram staining and speciation and antifungal susceptibility were performed with automated system VITEK 2.0.

Result: Out of 51 isolates, Candida auris was the most common species accounting for about 37.2% followed by C. albicans 19.7%, C. tropicalis 17.6%, and C. famata 9.8%. Candida auris has emerged as the predominant species during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. The incidence has risen from 22% to 60% during the pandemic. Candida species were found to be 96.08% sensitive to fluconazole, 94.12% to voriconazole, 90.19% to caspofungin/micafungin, 60.78% to amphotericin B, and 56.86% to flucytosine.

Conclusion: Candida auris has emerged as the predominant species in ICU setup and during SARS-CoV-2 pandemc. Empirical treatment with echinocandines would be appropriate in high-risk patients with suspected Candidemia.