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Studies on activity of azoles and essential oils alone and in combination against Cryptococcus neoformans clinical isolates

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Background: Fungal infections caused by *Cryptococcus neoformans* are a serious health concern for immunocompromised patients worldwide, and occasionally in immunocompetent subjects. Low-dose fluconazole and itraconazole are used as long-term maintenance therapy for cryptococcosis, whereas voriconazole and posaconazole are used as consolidation therapy. Many recent studies indicate that the widespread use of azoles, mainly fluconazole, is associated with the emergence of drug-resistant isolates, and related treatment failures. Besides, *C.neoformans* is intrinsically resistant to echinocandins and, to date, there are very few molecules with any activity towards *C.neoformans*, leading to heightened interest in finding new alternatives to conventional drugs for the treatment of mycosis caused by this yeast. Currently, new trends in drug discovery are represented by natural products from plants, or their extracts. Particularly, great interest in essential oils (EOs) as potential natural and economic alternatives or as adjuvants to conventional antifungal agents has emerged in recent years. In this study, we evaluated the antifungal activity of fluconazole, itraconazole and voriconazole in comparison with nine different EOs (fennel, lavender, lemon balm, pine, sage, thyme red-thymol chemotype, clove, oregano, geranium), and their main components (citronellal, ɣ-terpinene, linalylacetate, and terpinen-4-ol), against azole susceptible and not-susceptible *C.neoformans* isolates. Then, we investigated the effect of the association of itraconazole with EOs and EO components against *C.neoformans* isolates.

Material/methods: Seven *C.neoformans sensu lato* clinical isolates from HIV-infected patients were tested. The CLSI broth microdilution method was used to evaluate the susceptibility of *C.neoformans* either to azoles or to essential oils and their components, with some modifications for EO and

components. EOs composition was analysed by GC-MS. The chequerboard method was used for combination studies.

Results: Six *C.neoformans* isolates were susceptible to azoles, while one *C.neoformans* exhibited a reduced susceptibility to all tested azole drugs. Pine, oregano, clove, and thyme red EOs exhibited the highest antifungal activity with low MIC values. Among components, thymol, carvacrol, and α-pinene were high effective against *C.neoformans*. The results showed synergistic interactions (FICI<0.5) between itraconazole and oregano, pine, or thyme red against azole susceptible *C.neoformans* isolates. As regards the azole not-susceptible *C.neoformans* isolate, the synergistic effect with itraconazole was only observed with thyme red oil. Carvacrol was the most effective component, since strongly enhanced itraconazole activity against all *C.neoformans* isolates.

Conclusions: The results suggest that some EOs display high antifungal activity against *C.neoformans*, and suggest the potential effectiveness of thyme red, oregano EOs, and carvacrol, as adjuvants in combination with itraconazole. Further in-depth studies of the modes of action for synergistic combinations as well as *in vivo* preclinical models are encouraged to predict the translational use of these data for clinical settings.