TITLE: ANTIFUNGAL ACTION OF METAL COMPLEXES CONTAINING 1,10-PHENANTHROLINE AGAINST *Exophiala jeanselmei*

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ABSTRACT:

Exophiala jeanselmei is a dematiaceous fungus that causes phaeohyphomycosis, a disease with cutaneous, subcutaneous and disseminated infections. This mycosis is extremely difficult to treat and often refractory to various therapeutic approaches. Therefore, it is fundamental to search new antifungal agents to control and combat this fungal infection. In the last years, metal-based drugs have been a subject of great interest due to their therapeutic values and pharmacological applications. In this context, the aim of this study was to investigate the effect of fourteen (**1**-**14**) metal complexes of 1,10-phenanthroline-based compounds on *E. jeanselmei* growth. Antifungal susceptibility testing was performed using the M38-A2 document for filamentous fungi as described by (CLSI, 2008), with some modifications. All tested compounds were able to inhibit *E. dermatitidis* growth especially those with Ag^+ as metal ion. Thus, Ag^+ compounds coordinated to 1,10-phenantroline complexed to 3,6,9-trioxa-undecanodioic acid (**13**), and complexed to perchlorate salt (**14**) were effective in inhibiting fungal proliferation with MICs of 0.19 and 0.78 µM, respectively. In addition, the fungus was also sensitive to Ag^+ (**9**) and Cu^{2+} (**10**) compounds complexed to perchlorate salt coordinated to 1,10-phenanthroline-5,6-dione, both with MIC equal to 0.78 µM. Furthermore, these compounds (**9, 10, 13** and **14)** were able to exerted fungicidal effect against *E. dermatitidis*. The effect of the association between derivative **9** and classical antifungal drug itraconazole on *E. jeanselmei* growth was also determined. The results suggested that drug-drug interaction had an additive effect, since the fractional inhibitory concentration index value was equal to 0.62. Considering *E. jeanselmei* was sensitive to **9** and **10** derivatives, these compounds were chosen for *in vitro* interaction with human macrophage cell line THP-1. After treatment with both compounds in non-cytotoxic concentrations, THP-1 cells were lysed and the number of fungal colony-forming units (CFU) was defined. Our results indicated that the **9** and **10** derivative treatment was able to reduce the conidia viability after interaction with human macrophages. Taken together, our data contribute to the study of metal-based drug effect on dematiaceous fungi and add new insights into the possibility of exploiting these compounds in the future models of mycoses treatment.

Keywords: Phaeohyphomycosis, *Exophiala jeanselmei*, metal-based drugs, antifungal activity.

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