TITLE: SILVER(I) 1,10-PHENANTHROLINE-BASED DRUGS IMPACT ON THE GROWTH AND PEPTIDASE ACTIVITY OF *Fonsecaea pedrosoi* AND ITS INTERACTION WITH HUMAN MACROPHAGE

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ABSTRACT:
Fonsecaea pedrosoi is a dematiaceous filamentous fungus and the main chromoblastomycosis etiological agent. This study aimed at assessing the effect of **14** compounds derived from 1,10-phenanthroline coordinated to transition metals (silver, copper or manganese) complexed to different carboxylic acids, and to the perchlorate salt on *F. pedrosoi*. The antifungal susceptibility testing of filamentous fungi (document M38-A2, CLSI 2008) showed that most of them were able to inhibit the *F. pedrosoi* proliferation with minimum inhibitory concentration (MIC) values, which ranged from 0.62 to 100 μM. Among the derivatives tested, the most effective on fungal growth inhibition were the silver-coordinated 1,10-phenanthroline compounds complexed to the perchlorate salt (**12**), and 3,6,9-trioxa undecanodioic acid (**14**), showing MIC values equal to 1.25 and 0.62 μM, respectively. Our research group showed metallopeptidase and aspartic peptidases produced by *F. pedrosoi* are involved with its biology and/or pathogenesis. Thus, the effect of compounds **12** and **14** on these enzymatic activities was evaluated using fluorogenic substrates. Both compounds inhibited fungal metallo and aspartic peptidase activities by around 50%. In addition, we assessed their action on *F. pedrosoi* after interaction with human macrophages derived from THP-1. The effect of compounds on the viability of macrophages was determined using 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) reduction assay. The results showed the macrophages remained nearly 90% viable after treatment with both compounds, when their concentrations were ≤ 1.25 and 0.62 μM, respectively. Simultaneously, fungal cells were incubated with THP-1 for determining the macrophage killing rate. After 1 h, the non-associated fungal cells were removed and the system treated for 20 h with different non-cytotoxic concentrations of both compounds. Our data revealed that only the conidia treated with compound **12** were susceptible to macrophages, since only 50% of fungal cells remained viable after colony-forming units assay. Taken together, our data corroborate the antifungal action of these derivatives and suggest these compounds may represent a future metallopharmaceutical option against chromoblastomycosis.

Keywords: chromoblastomycosis, metal-based drugs, antifungal activity, cellular interaction

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