TITLE: THE ACTION OF SILVER COORDINATION COMPOUNDS WITH ANTIMICROBIAL PROPERTIES ON PATHOGENIC FUNGUS *Fonsecaea pedrosoi*

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ABSTRACT:

Fonsecaea pedrosoi, a dematiaceous filamentous fungus is the main chromoblastomycosis (CBM) etiologic agent. The treatment of this subcutaneous mycosis is difficult; the currently available therapies have several side effects and reports of relapses, as well as antifungal resistance. Metallic complexes derived from 1,10-phenanthroline demonstrated potential therapeutic action against microbial infections. The aim of this study was evaluate the effect of 1,10-phenanthroline derivatives of silver coordinated to perchlorate salt (**1**) and coordinated to carboxylic acid, 3,6,9-trioxa-undecanoic acid (**2**) on the fungal growth and enzymes activities produced by *F. pedrosoi*. The antifungal activity of the compounds was carried out using the broth microdilution assay, as described by CLSI, document M38-A2. The compounds **1** and **2** were able to inhibit the growth of *F. pedrosoi*, presenting minimum inhibitory concentration (MIC) values equal to 2.50 and 1.25 µM, respectively. In addition, both compounds showing fungicide effect on *F. pedrosoi* growth. Our research group showed that aspartic peptidase and ecto-phosphatase produced by *F. pedrosoi* are involved with biology and pathogenesis of this fungus. Thus, the effect of compounds **1** and **2** on these enzymatic activities was investigated using fluorogenic peptide substrate (peptidase) and chromogenic substrate *p*-nitrophenylphosphate (phosphatase). The derivatives **1** and **2** were able to inhibit the aspartic peptidase activity of *F. pedrosoi* by around 50%. However, the derivatives did not affect the ecto-phosphatase activity produced by *F. pedrosoi*. Moreover, the interaction between the compounds and classical antifungals (itraconazole (ITC) and amphotericin B (AMB)) was determined using checkerboard assay and fractional inhibitory concentration index (FICI) calculation. The FICI values obtained with the combinations **1**-ITC, **1**-AMB, **2**-ITC and **2**-AMB were 1.0; 1.0; 1.0 and 0.6, respectively. Thus, the results revealed that compounds association with both antifungal agents presented additive effect. Taken together, our results corroborate that coordination compounds represent a promising antifungal drugs effective at inhibiting also *F. pedrosoi* growth.

Keywords: chromoblastomycosis, *Fonsecaea pedrosoi*, metal-based drugs, cellular growth.

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