

TITLE: EVALUATION OF THE ANTIFUNGAL EFFECT OF METAL-AZOLES COMPLEXES ON PLANKTONIC CELLS AND BIOFILMS OF *Candida sp.*

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ABSTRACT

Candida species are important agents of superficial and disseminated opportunistic fungal infections. *Candida sp.* yeasts possess the ability to form biofilm, a community of microorganisms that grow adhered to biotic and abiotic surfaces covered by an extracellular matrix. Biofilms are less susceptible to antifungal agents, complicating the treatment of these infections. Imidazole derivatives and triazoles are the main antifungals used to treat infections caused by *Candida sp.*, but they are ineffective against biofilms. Previous studies have shown that transition metals complexed to imidazole derivatives have an effect on *Saccharomyces cerevisiae*. Thus, the objective of this work was to evaluate the antifungal activity of organometallic complexes associated with azole compounds on planktonic cells and biofilms of *Candida glabrata* and *Candida albicans*. For this work, Fluconazole (FLC), Itraconazole (ITR), Clotrimazole (CTZ) and Ketoconazole (KTZ) pure or complexed to gold (Au), zinc (Zn) were used. Standard antifungals and starting salts were used as experimental controls. The activity on planktonic cells was evaluated by broth microdilution assays, according to document M27-A2, and biofilms with protocol of the group. The lowest concentration of each drug capable of inhibiting 50% and 100% of planktonic cell growth (MIC₅₀ e MIC₁₀₀) or the metabolic activity of biofilms (BMIC₅₀ e BMIC₁₀₀) was determined by spectrophotometry, 490 nm. Furthermore, the inhibitory activity of the complexes in biofilms formed on fragments of sterile human nails was performed according to the protocol described previously and the effects are being evaluated by scanning electron microscopy (SEM). Planktonic cells were susceptible both to CTZ alone and to complexes with zinc and gold, with MIC₁₀₀ close to or smaller than the corresponding antifungal alone, with emphasis on ZnAcITR (0.25-1µg/mL) and AuCTZCl (0,008-0,03µg/mL). Complexation with gold did not increase the antifungal activity of KTZ and similar values (MIC₁₀₀) were found for complexes and antifungal alone. In biofilms, AuCTZ (64-128µg/mL) and ZnAcCTZ (32-64µg/mL) showed the best inhibitory results, with lower BMIC₅₀ than the antifungal alone (KTZ and CTZ, 256µg/mL for both). We have demonstrated, therefore, that azoles complexed to gold and zinc, especially ketoconazole, present antifungal activity against both planktonic cells and biofilms of *C. albicans* and *C. glabrata*.

Keywords: Antifúngicos; *Candida*; Micologia; Microbiologia

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