TITLE: ACTIVITY OF THE FLAVONOID BAICALEIN AND FLUCONAZOLE AGAINST PLANKTONIC CELLS, PRE-ADHERED CELLS AND BIOFILM OF *CANDIDA PARAPSILOSIS* STRICTO SENSU ISOLATES**.**

AUTHORS: FERNANDES, M.M.F.S[1].; SOUZA, C.M[1].; PRADO, L.A[1].; COSTA, V.G[1].; PERINI, H.F[1].; SANTOS, R. C[1].; FURLANETO-MAIA, L[2].; FURLANETO, M.C[1].

INSTITUTION: [1]UNIVERSIDADE ESTADUAL DE LONDRINA (RODOVIA CELSO GARCIA CID, KM 380, S/N - CAMPUS UNIVERSITÁRIO, LONDRINA - PR, CEP: 86057-970). [2]UNIVERSIDADE TECNOLÓGICA FEDERAL DO PARANÁ - UTFPR (ESTR. DOS PIONEIROS, 3131 - CENTRO, LONDRINA - PR, CEP: 86020-430).

ABSTRACT:

Candida parapsilosis is one of the main fungal agent responsable for nosocomial human infections. Considering the capability of this species to form biofilm and the occurrence of adquired resistance to antifungals, the search for new antifungal therapies is in course. The aims of this study were to evaluate the antifungal activity of the flavonoid baicalein and fluconazole alone and combined against planktonic cells of blood isolates of *C. parapsilosis* stricto sensu, to analyse morphological alterations at ultrastructural level conferred by baicalein, fluconazole and the combined compounds and to evaluate the activity of fluconazole and baicalein against pre-adhered cells and biofilm. The CIM_{50} value for baicalein was 8µg/ml against planktonic cells of fluconazole-resistant isolates and 4-8 µg/ml against fluconazole-susceptible isolates. The combined fluconazole and baicalein resulted in synergism for the fluconazole-resistant isolate 357 e for the fluconazole-susceptible isolate 551 considering CIM_{50}. There was reduction in the concentration of CIM_{50} for at least one of the compounds for the majority of tested isolates. The ultrastructural analyses revealed that for the isolate where synergism between fluconazole and baicalein occurred the morphogenesis was affected with the presence of extracellular matrix, including matrix interconecting cells following exposure to combined compounds. For the isolate where the combined action of compounds was indifferent the morphogenesis was not affected, with presence of large amounts of matrix following treatment with baicalein, besides, the exposure to both compounds resulted in cellular alterations indicative of cell membrane damage. Considering pre-adhered cells the majority of the isolates exhibited lower susceptibility to fluconazole where 25% of the fluconazole-susceptible isolates and 83% of fluconazole-resistant isolates showed $CIMA_{50}$ >200 µg/ml. The compounds did not showed inhibitory effect against biofilm of the majority of the isolates tested, e.g., 75% and 86% of the isolates showed $CIMB_{50}$ de >800 µg/ml for fluconazole and baicalein, respectively. The data show the potential of baicalein as antifungal agent against planktonic cells of *C. parapsilosis* isolates, independent of their susceptibility to fluconazole. This study showed that early biofilm stage exhibited lower susceptibility to both fluconazole and baicalein compared to planktonic cells.

Keywords: *Candida parapsilosis,* biofilm, antifungal activity, fluconazole, baicalein.

Development Agency: CAPES, CNPq