TITLE: EVALUATION OF ANTIFUNGAL ACTIVITY AND CYTOTOXICITY OF HISTATIN-5 DERIVATIVES FOR THE TREATMENT OF ORAL CANDIDOSIS.

AUTHORS: SOUZA, R.C.R.O; GIAMPAOLO, E.T; GARRIDO, S.S; MACHADO, M.A.A.M; SIQUEIRA, W.L; MOFFA, E.B.
INSTITUTION: UNIVERSIDADE CEUMA- RUA JOSUÉ MONTELO, 01, RENASCENÇA II-SÃO LUIS –MA-CEP: 65075120

ABSTRACT: The continuous use of topical and systemic antifungals for conventional treatment of oral candidosis has resulted in the appearance of resistant strains of *Candida albicans*. For this reason, new technologies for drug development, such as biopharmaceuticals, are an innovative strategy because of their promising mechanism of action in the field of biotechnology. *C. albicans*, a pathological agent of fungal origin, expresses several virulence factors and is commonly found in oral cavity, and can affect people of different ages, immunologically compromised, or who use dental prostheses. Histatin-5 (Hst-5) is a peptide of human saliva with strong fungicidal properties. This peptide is extremely rich in histidine and lysine and, at physiological pH, has the potential to inhibit the formation of *C albicans* biofilm, and can therefore be applied in the treatment of oral candidosis. In view of the above, this study proposes evaluate the efficacy of Hst-5 and two dimers in the inhibition and inactivation of C. albicans biofilm formed on the basis of removable prostheses, the cytotoxicity of solutions on gingival fibroblasts and he synergistic effect of Hst-5 and Nystatin in the inactivation of *C. albicans*. The peptides were developed synthetically by the solid phase organic synthesis method. These structural modifications were proposed in order to optimize the therapeutic potential of the biopharmaceutical, to reduce the resistance of the microorganisms, as well as their toxicity and adverse effects and to promote greater adherence to the treatment by the patient. The purification was carried out by the HPLC method, followed by characterization of the same in a mass spectrometer. The second part of the study consists of performing in vitro tests, XTT assay and countable viable colonies; determination of concentration to promote inactivation of microorganisms, through the same tests described above and evaluation of peptide cytotoxicity. Data were submitted to analysis of variance with significance level of 5%. Our analyzes indicate that Hst-5 and its derivatives exhibited similar antifungal activity during microbiological assays. However, the MTT and SEM tests showed that the Hst-5 derivative, where there was the substitution of the serine amino acid for cysteine, had a lower cytotoxic effect in relation to the others. In addition, our results show the synergistic effect of Hst-5 and Nystatin, where the combination of two drugs, even at sub-inhibitory concentrations, was able to cause complete inactivation of *C. albicans*. Thus, a small modification in the amino acid sequence of Histatin-5 may generate a protein with a similar but less cytotoxic antifungal potential and that histatin may potentiate the effect of commonly used drugs in clinical practice. These analyzes will provide a basis for the possible development of a new protocol for the treatment of candidiasis in users of removable prostheses.

KEY WORDS: *C. albicans; Saliva; Histatin-5; Peptides; Antifungals.*
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