

Title: Antifungal activity of Nimesulide isolated or in combination with Terbinafine against dermatophytes and its possible action mechanism *in vitro*.

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Abstract

Dermatophytes has shown resistance to current antifungal drugs, as terbinafine, and this has led to research new compounds as an alternative therapy. Thus, this study evaluated the antifungal action of non-steroidal anti-inflammatory drug (NSAID), Nimesulide, alone or in combination with terbinafine against dermatophytes fungi, and investigated the role of prostaglandin E2 (PGE2) and urease in this action. The antifungal activity of Nimesulide was tested against *Trichophyton mentagrophytes* ATCC 9533 and clinical isolates *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Epidermophyton floccosum* and *Microsporum canis*. To assess the antifungal activity of terbinafine, nimesulide and the role of PGE2 and urease was used the microdilution assay with Resazurin staining to determine the Minimum Inhibitory Concentration (MIC) and the methods of growing in petri dishes with counting units forming colonies to obtain the Minimum Fungicidal Concentration (MFC). Our data showed that Nimesulide had excellent fungicidal action against the *T. mentagrophytes* ATCC 9533, with MIC values (0.002 µg/mL) and CFM (0.008 µg/mL) similar to those found for terbinafine. However, to clinical isolates of *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Epidermophyton floccosum* and *Microsporum canis*, this antifungal effect was not so pronounced, because the MIC and CFM values of Nimesulide to these fungi ranged between 400 to 0.112 µg/mL. Thereby, the role of urease and PGE2 in antifungal activity induced by nimesulide was performed with the strain of *T. mentagrophytes* ATCC 9533, and results demonstrated that the the PGE2 and urease were able to reverse the inhibition of fungal growth induced by NSAID. In addition, data of combination of Nimesulide and terbinafine showed an inhibitory effect of the fungal growth in 9:1 drugs ratio, i.e 0.0002µg/mL of Terbinafine and 0.0018 µg/mL of Nimesulide, showing an indifferent result in Fractional Inhibition Index. From these data, we conclude that the Nimesulide showed good antifungal activity against dermatophytes, which it can be associated the PGE2 and urease production. However, molecular modeling studies should be conducted to improve the selectivity of this compound and this activity.

Keywords: Dermatophytes, Prostaglandin E2, Cyclooxygenase, urease, Nimesulide.

Agência de Fomento: CNPq, FAPESPA, UFPA