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SYNERGIC EFFECT OF METRONIDAZOLE IN COMBINATION WITH AZOLE DERVATIVES AGAINST GROWTH OF *LEISHMANIA TROPICA* PROMASTIGOTES

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ABSTRACT : The growth inhibitory effects of azole derivatives were tested against promastigotes of *L. tropica*. Ketoconazole, Itraconazole, Nystatin, Clotrimazole and Terbinafine at concentration of 1mM inhibited 70%, 77%, 53%, 39% and 72% respectively, growth of promastigotes whereas Fluconazole at 25mM and Metronidazole at 0.5mg inhibited 78% and 43% respectively growth of promastigotes. The synergistic conditions of combination of Metronidazole with azole derivatives showed higher growth inhibition of *L. tropica* promastigotes suggesting the increasment of the efficacy of dual drug therapy. Treatment of *L. tropica* promastigotes with azole derivatives were not resulted in decreasing in the amount of protein and nucleic acid contents. In contrast, the azole derivatives resulted in the inhibition of the enzyme lanosterol reductase. The postulated possibility of the inhibitory effect of azole derivatives may be due to blocking of the synthesis of ergostrol through inhibition of reductase that is present in the plasma membrane resulting in destructive proliferation thus causing death of the parasite.

Key words : Synergic, metronidazole, azole, *Leishmania*.

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INTRODUCTION

Glucantime and Pentostam are generally the therapeutic agents of choice, for treatment of leishmaniasis, but both appear to have similar toxicity and therapeutic value (Loiseau *et al*, 2020). In certain instances, the disease is unresponsive to antimonials, and alternative drugs, Pentamidine and Amphotericin B, have to be used. Both have serious toxicity problems, the Pentamidine causing diabetes mellitus and kidney damage whereas the Amphotericin B being highly nephrotoxic (Valle *et al*, 2019).

The deficiencies of the present antileishmanials are a stimulus for search in to new treatments. An alternative approach to drug development is via, the drug combination for treatment for drug resistance conditions. The combination treatment of pentavalent antimonials with Miltefosine is recommended as treatment regimens for leishmaniasis in some countries (Ventin *et al*, 2018). The differences in sterols in *Leishmania* and Man suggest that there would be differences in the biosynthetic pathways, which would allow therapeutic attack in this area of metabolism (Raj *et al*, 2020). There is indeed an established antimycotic antisterol synthesis agent, Ketoconazole, which is active against *Leishmania* (Lima *et al*, 2020), it has been demonstrated that ketoconazole inhibits demethylation of sterols in *L. mexicana* promastigotes (Nunes *et al*, 2017 and Galvao *et al*, 2017) and can be used as potential chemotherapeutic agents for the treatment of leishmaniasis.

Thus, the present investigation aimed to find out the experimental assessment of azole antifungal agents Ketoconazole, Itraconazole, Fluconazole, Nystatin, Clotrimazole and Terbinafine for antileishmanial activity *in vitro*. The present study also aimed to find out the molecular and biochemical analysis of *Leishmania tropica* promastigotes following treatment with azole drugs.

MATERIALS AND METHODS

Leishmania growth

Promastigotes of *Leishmania tropica* were grown in modified Tobies medium at 26°C as described by Chang and Hendricks (1985).