Combination therapy using amitriptyline with amphotericin B and miltefosine against in *vitro* cutaneous leishmaniasis

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Leishmaniasis is a disease that ranges from localized skin ulcers to a lethal systemic disease. An estimated 0.7 – 1.2 million new cases and 20 – 30 thousand deaths occur each year. Cutaneous leishmaniasis is the most common form of disease, causing skin lesions as cutaneous ulcerations in exposed parts of the body. The therapy has serious drawbacks in terms of safety, resistance, stability, and cost; additionally, it has low tolerability and long treatment duration. The search for novel drugs against neglected diseases using drug repurposing and combined therapy approaches continue to be an excellent opportunity to reduce time and costs of research. In this work, amitriptyline, an oral antidepressant drug, was *in vitro* associated with amphotericin B and miltefosine against *Leishmania* (L.) *amazonensis*. Promastigotes and intracellular amastigotes were used to calculate the 50% inhibitory concentration values. Drug interactions were assessed with a modified fixed ratio isobologram method and Fractional Inhibitory Concentrations (FIC), sum of FIC (ΣFIC) and overall mean ΣFIC were calculated for each combination. The nature of interactions was classified according to the overall mean ΣFIC. The mean ΣFIC values of combination between amitriptyline and standard drugs ranged from 1.03 to 1.78, indicating indifferent interactions. Graphical isobologram analysis showed that the combination of amitriptyline and miltefosine was the most promising, presenting the smallest mean ΣFIC value. Future studies using murine models can be investigated, as no antagonism was found in the *in vitro* combination.

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