EVALUATION OF U18666A EFFECTS ON THE STEROL METABOLISM OF *LEISHMANIA SPP.*

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Leishmaniasis is a neglected tropical disease that poses a major global public health challenge, particularly due to increasing resistance and therapeutic failures of current treatments. *Leishmania spp.*, the causative agent of leishmaniasis, relies on sterol metabolism for survival, making this pathway a potential therapeutic target. U18666A is known to inhibit cholesterol biosynthesis and transport in mammalian cells, but its effects on trypanosomatids remain unexplored. This study aimed to evaluate the impact of U18666A on the sterol metabolism of *Leishmania* spp. The compound demonstrated significant antiproliferative activity against *L. amazonensis* promastigotes and amastigotes, with IC_{50} values below 1 µM. Importantly, U18666A exhibited no toxicity in murine peritoneal macrophages at concentrations up to 24 µM. Ultrastructural analysis revealed progressive organelle alterations in treated parasites, suggesting inhibition of intracellular sterol trafficking. Additionally, gas chromatography-mass spectrometry (GC-MS) analysis suggested that U18666A disrupts sterol biosynthesis at multiple points, including sterol C14α-demethylase (CYP51) and sterol C4-methyl oxydase (CYP5122A1), the latter being a recently described enzyme in *Leishmania*. Furthermore, co-treatment with ezetimibe, a cholesterol absorption inhibitor, showed an additive effect, highlighting the potential of drug combination strategies against leishmaniasis. These findings enhance our understanding of parasite biochemistry and open new perspectives for the development of more effective therapeutic approaches for leishmaniasis