SEARCH FOR LEISHMANIA CYP450 INHIBITOR DRUG AS A REPOSITIONING STRATEGY

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The treatment of leishmaniasis is primarily based on the use of pentavalent antimonials. Drugs such as pentamidine and amphotericin B, originally developed for other diseases, have been repurposed for this condition. However, these drugs are associated with side effects, high toxicity, and resistance. The development of new drugs requires significant investment, whereas drug repositioning offers a cost-effective alternative to address public health needs. Enzymes of the cytochrome P450 complex (CYP450) play a crucial role in the metabolism of xenobiotics and are involved in key metabolic processes, such as sterol and fatty acid biosynthesis. Some studies suggest that inhibitors of CYP51 in *Leishmania* spp. could serve as a viable therapeutic strategy. Based on this, our study hypothesizes that drugs inhibiting human CYP450 may exhibit leishmanicidal activity by targeting enzymes of the same complex in *Leishmania* spp., whether they have already been described or not. Recently, our group identified three additional enzymes belonging to this complex, annotated in the *Leishmania infantum* genome as putative CYP types. Using molecular biology techniques, we confirmed the presence of these transcripts in the *Leishmania amazonensis* genome. In this context, 27 licensed drugs from a library of CYP450 inhibitors were tested, and 11 demonstrated leishmanicidal activity in promastigotes. Among these, ritonavir, efavirenz, and saquinavir exhibited IC_{50} values of 3.1µM, 2.8µM, and 3.0µM in amastigotes, respectively. Cytotoxicity assays conducted in murine macrophages determined CC_{50} values of 69.2µM, 39.7µM, and 45.2µM for these drugs, respectively, indicating a selectivity index greater than 10 for all three. To confirm whether their mechanism of action involves CYP450 inhibition, these drugs will be analyzed using a commercial kit, with the microsomal fraction of *Leishmania* serving as the CYP450 source. The remaining selected drugs are currently undergoing testing in amastigotes.

Supported By Oswaldo Cruz Instituto Fiocruz (FIOCRUZ).

Keywords: Leishmaniasis, CYP450, repositioning.