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2'-HYDROXYFLAVANONE ACTIVITY AGAINST WILD-TYPE AND ANTIMONY-RESISTANT *Leishmania infantum* AND ITS PROOXIDANT PROPERTY AS A POSSIBLE MECHANISM OF ACTION

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Abstract

Pentavalent antimonials, the first line choice of Leishmaniasis treatment, are becoming ineffective due to parasitic resistance, the main limitation associated with its use. Visceral Leishmaniasis (VL), the most severe clinical manifestation of Leishmaniasis can be fatal in 95% of untreated cases. Therefore, the search for new alternatives for Leishmaniasis treatment is crucial. Natural products, such as flavonoids, are known for their prooxidant properties, inducing reactive oxygen species (ROS) that can be associated with cellular damage and death, and have been described as potent antileishmanial candidates. 2'-hydroxiflavanone (2HF) had already been described as a promising molecule against antimony-sensitive and -resistant *L. amazonensis* in a murine model of Cutaneous Leishmaniasis. This study evaluated the 2HF *in vitro* activity and its prooxidant effect as a possible mechanism of action against wild-type (WT), antimony-sensitive (S), and -resistant (R) *L. infantum*. WT, S, and R promastigotes were incubated with 2HF (0–96µM) for 72h. 2HF inhibited WT, S, and R promastigotes in a concentration-dependent manner, demonstrating an IC_{50} of 6.9; 11.57, and 20.24µM, respectively. To evaluate if the 2HF action is linked to ROS generation, promastigotes were treated with 2HF and incubated with 20µM of H_2DCFDA. 2HF promoted an increase in ROS levels in a concentration-dependent manner, reaching respectively a 1.9, 1.7, and 1.6 fold increase at the highest concentration of 2HF (96µM) compared to control. In the antiamastigote assay, WT *L. infantum* infected macrophages were treated for 72h with 2HF, showing a concentration-dependent reduction in the infection index, with an IC_{50} of 4µM. The selectivity index was 21,87. These results indicate 2HF as a potential candidate for VL treatment, reinforcing its ability to overcome resistance issues and its prooxidant activity, highlighting the need for further studies exploring mechanisms of action and *in vivo* efficacy.

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