Effects of metal-coordinated compounds on the physiology of *Leishmania amazonensis* and *Leishmania chagasi*

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Leishmaniasis is a disease caused by flagellated protozoa belonging to *Leishmania* genus. The drugs used in its treatment present serious problems and the search for anti-*Leishmania* compounds remains a major goal. In this context, our objective is to evaluate the effects of metal-coordinated Ag^{+}-*phendione* and Cu^{2+}-*phendione* compounds as potential drugs to be used in a chemotherapy against two of the most relevant *Leishmania* species in the country, *L. amazonensis* and *L. chagasi*. Our results showed that *L. amazonensis* and *L. chagasi* presented a dose-dependent reduction in growth in the presence of Ag^{+}-*phendione* and Cu^{2+}-*phendione*, being the IC_{50} value calculated for *L. amazonensis* as 7,8 nM and 7,5 nM, respectively. The same effect was observed on the growth of *L. chagasi*, being the IC_{50} calculated as 24 nM and 20 nM for Ag^{+}-*phendione* and Cu^{2+}-*phendione*, respectively. The optical scanning electron microscopy showed that the metal complexes caused relevant morphological changes in promastigotes, such as shortening of the cell body and shortening/loss of the flagellum. Additionally, Ag^{+}-*phendione* and Cu^{2+}-*phendione* were able to affect the mitochondrial metabolism as observed through MTT, as well as the mitochondrial membrane potential as evaluated by Rhodamine 123, besides promoting an increase in the production of reactive oxygen species. Our results showed that the treatment of the promastigotes with the metallocompounds was also able to promote a suspension of the cell cycle of the parasites, as evaluated through flow cytometry. In addition, fragmentation of the parasites DNA was verified by the TUNEL technique, as well as phosphatidylserine exposure, as assessed by Annexin V. The pre-treatment with Ag^{+}-*phendione* and Cu^{2+}-*phendione* inhibited the interaction of *L. amazonensis* and *L. chagasi* with THP1 cells; additionally, THP1 cells previously infected with *L. amazonenis* and *L. chagasi* and then post-treated with the metallocompounds presented a significant reduction in the viability of intracellular amastigotes. The results presented may contribute to the development of new drugs able to act in a selective and effective way against the diseases caused by *Leishmania*, being an alternative chemotherapy for leishmaniasis.

Keywords: leishmaniasis, metallocompounds, chemotherapy.

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