TITLE: COORDINATION COMPOUNDS AS POTENTIAL METALLODRUGS: A NEW THERAPEUTIC PROPOSAL AGAINST LEISHMANIOSE

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ABSTRACT:

Leishmaniases are diseases caused by flagellated protozoa belonging to *Leishmania* genus, representing a group of neglected diseases considered relevant in the Brazilian scenario. The drugs used in the treatment of leishmaniases present serious problems, including high toxicity and side effects, emergence of resistant strains and high cost of the compounds and the search for compounds with anti-leishmania activity remains a major goal. In this context, it is the purpose of our group to evaluate the *in vitro* effects of metal-coordinated Ag-*phendione* and Cu^{2+}-*phendione* compounds as potential drugs to be used in an effective chemotherapy against two of the most relevant *Leishmania* species in the country, *L. amazonensis* and *L. chagasi*, the ethiologic agents of cutaneous and visceral leishmaniasis, respectively. 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 0,69 μM and 0,52 μM for Ag-*phendione* and Cu^{2+}-*phendione*, respectively. The optical microscopy analysis has shown that both Ag-*phendione* and Cu^{2+}-*phendione* caused diverse morphological changes in *L. amazonensis* and *L. chagasi*, such as decreasing of the cell size, parasite rounding, accumulation of granules in the cytoplasm and nucleus duplication. In addition, the treatment with the Ag-*phendione* and Cu^{2+}-*phendione* modulated the expression of gp63 and CPB important surface molecules of the parasite, which act as virulence factors. The effect of these compounds was also evaluated in the interaction process with RAW macrophages and in the survival of intracellular parasites. The pre-treatment with Ag-*phendione* and Cu^{2+}-*phendione* inhibited the interaction of *L. amazonensis* with RAW macrophages in a dose-dependent manner. Additionality, the post-treatment with Ag-*phendione* and Cu^{2+}-*phendione* of RAW cells previously infected with *L. amazonenis* significantly reduced the viability of intracellular amastigotes (IC_{50} = 0.89 μM). Altogether, 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: *Leishmania*, chemotherapy, metallodrugs
Development Agency: CNPq, FAPERJ, CAPES.