New compounds derived from the Brazilian biodiversity presenting low toxicity and high *in vitro* antileishmanial efficacy against different *Leishmania* species

Grasiele S.V. Tavares[1]; Mariana C. Duarte[1,2]; Vívian T. Martins[1]; Daniela P. Lage[1]; Lourena E. Costa[1]; Miguel A. Chávez-Fumagalli[1]; Daniel S. Dias[1]; Thaís T.O. Santos[1]; Beatriz C.S. Salles[1]; Patrícia A.F. Ribeiro[1]; Fernanda F. Ramos[1]; Mariana P. Lima[1]; Danniele L. Vale[2]; Débora V.C. Mendonça[1]; Daniel Menezes-Souza[1,2]; Bruno M. Roatt[2]; Wiliam C.B. Régis[3]; Eduardo A.F. Coelho[1,2]

[1]Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical, Faculdade de Medicina, UFMG, Brazil. [2]Departamento de Patologia Clínica, COLTEC, UFMG, Brazil. [3] PUC Minas, Belo Horizonte, MG, Brazil.

Leishmaniasis is a neglected disease that presents a high incidence in Brazil. The drugs of choice for the treatment of the disease are the pentavalent antimonials that may induce to renal and cardiac toxicity. The purpose of this study was to identify new and safe alternative treatments against leishmaniasis based on natural products of the Brazilian flora. The aqueous extract of *Agaricus blazei* Murill was fractionated in AMICON® filters and five purified fractions were obtained. Biochemical characterization of fractions was performed by SDS-PAGE and mass spectrometry. The death rate in *Leishmania* induced by the fractions was evaluated by MTT assays in promastigotes and *like*-amastigotes forms of *L. amazonensis*, *L. chagasi* and *L. major*. The fractions were tested for citotoxicity in murine macrophages and in the treatment of the infected macrophages with *Leishmania*. The aqueous extract of *Agaricus blazei* Murill showed a significant death rate (about 50%) against promastigotes and *like*-amastigotes forms of the three parasite species. The fraction namely F5 showed the best antileishmanial activity when used in a low concentration (5 µg) inducing the viability loss in 60% of promastigotes and 90% of *like*-amastigotes forms. The fractions presented no cytotoxicity into murine macrophages and no nitric oxide production, indicating the existence of a direct mechanism of death of the parasites. The results showed that the aqueous extract and purified fractions of *A. blazei* have significant death rate in different *Leishmania* species, present no toxicity to murine macrophages and are effective in inducing the killing of internalized parasites. The death rate presented by *Leishmania* species in presence of the *Agaricus blazei* fungus provides good perspectives for the drug development obtained from natural and non-cytotoxic products.

Keywords: *Agaricus blazei* Murill; treatment; antileishmanial activity; toxicity; Brazilian biodiversity; leishmaniasis.

Financial Support: Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical, Faculdade de Medicina, UFMG. FAPEMIG. CAPES. CNPq.