

Title: Evaluation of the leishmanicidal activity and the modulation of the infection of murine macrophages infected with *Leishmania amazonensis* and treated with nerol

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ABSTRACT: Leishmaniasis is among the most important neglected diseases in the world. It is a parasitic disease transmitted by the female of a vector called sand fly. The transmission of the disease occurs during the blood meal of the female of this vector, which deposits infective forms in the vertebrate host and thus triggers the infection. Depending on the immune response and the nutritional and health status and the species incriminated in the infection, the disease can trigger from localized skin presentations to more significantly severe visceral changes, which, when untreated, become fatal. Treatments used as first choice, such as Glucantime® and Sodium Stibogluconate, and second choice treatments, such as Amphotericin B, have many adverse effects, long treatment time, in addition to the appearance of parasites resistant to drugs. The search for new therapeutic compounds with leishmanicidal potential and that have fewer side effects has guided the most recent research. With this, our study directed efforts towards an alternative treatment with a secondary metabolite of a product of plant origin, using an essential oil derivative called nerol, a monoterpene widely used in perfumeries and already with recognized biological applicability, to mention as an antifungal, anxiolytic, cardioprotective and protozoaricide. To evaluate the leishmanicidal action, different concentrations of nerol (from 3.25 µg/mL to 100 µg/mL) were tested in cultures of promastigotes (2×10^6 parasites/ml) placed in a 96-well microplate, with dilutions made in quadruplicate. After incubating the promastigotes, the leishmanicidal activity of the drug was evaluated using the Resazurin colorimetric method. The potential modulation of infection with different concentrations of nerol (12.5 µg/mL to 400 µg/mL) was performed in cultures of murine peritoneal macrophages infected with amastigotes of *Leishmania amazonensis*, placed in a 24-well plate, for a period of 24 hours, and having Glucantime® as a positive control. The last factor to be analyzed was the cytotoxicity of the drug in mammalian cells, with peritoneal macrophages placed in a 96-well plate (2×10^4 cells / well) with cell viability determined by the MTT colorimetric method, aiming to measure drug safety. Nerol showed an excellent leishmanicidal potential in flagellated forms (promastigotes), with a dose-dependent reduction in the viability of these promastigotes, with a concentration of 25 µg/mL showing a reduction of more than 65% in viability compared to the group without treatment, in addition to being able to reduce the infection rate at all concentrations tested by at least 46% compared to the negative control, with moderate cell viability, reducing the parasite load at all concentrations of nerol when compared to the control without treatment and to the positive control with Glucantime®, thus presenting biologically interesting results, making room for new research on the mechanisms involved in the cytotoxicity of nerol, in order to improve its therapeutic use.

Keywords: Leishmania, nerol, treatment, therapeutic alternatives