TITLE: EVALUATION OF PCM PULMONARY HISTOPATHOLOGICAL ASPECTS IN MURINE MODEL AFTER TREATMENT WITH NEW CP1 COMPOUND

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ABSTRACT:
Paracoccidioidomycosis (PCM) is a mycosis with granulomatous character, responsible for approximately 51.2% of the deaths caused by systemic mycoses in Brazil whose main etiological agent is *Paracoccidiodes brasiliensis*. Although the PCM treatment with conventional antifungal be effective, the main limitation is the needed of treatment long periods which ultimately amplifies the side effects and toxicity. Itraconazole (ITZ) is one of the most common antifungal used; however, studies have shown this drug is not able to control the pulmonary fibrotic sequels, presented in about 60% patients even after treatment. In search for new antifungal drugs, *in silico* methods are largely used to optimize the identification and development of new selective drugs. The new CP1 compound was selected for presenting promising *in vitro* antifungal activity. Thus, the aim of this study was to evaluate the CP1 effect in the treatment of experimental PCM in murine model by analyzing histopathological aspects. Male Balb/c mice were infected intratracheally ($1x10^6$ yeast/mouse). After 48 h, the animals were intraperitoneally treated with CP1 (5 mg/Kg), itraconazole (5 mg/Kg) or vehicle (PBS, DMSO and Pluronic) for 14 days (1x per day). The animals were then euthanized; the lungs were removed, fixed in PBS-formalin 10%, dehydrated and embedded in paraffin. Sections of 5 µm were stained with hematoxylin-eosin (H&E). The histopathological analysis suggests that CP1 were able to significantly reduce the tissue damage caused by *P. brasiliensis* infection when compared to the groups treated with ITZ or vehicle. A semiquantitative analysis indicated that animals treated with CP1 not showed tissue damage level III (major tissue impairment), also was not observed pulmonary fibrosis, inflammatory infiltrates or granulomas (level III). However, 60 % of the animals from ITZ group presented pulmonary fibrosis and 40% presented inflammatory infiltrated (level III). In the group treated with the vehicle, 60% of them presented pulmonary impairment level III, pulmonary fibrosis, inflammatory infiltrate and fungi cells. Although there were fungi cells in all groups, CP1 group was highlighted by the absence of yeasts in 40% of the animals. Thus, the results showed that CP1 had a great therapeutical potential due to its important antifungal activity, mainly for the control of the PCM pulmonary sequels.

Keywords: Murine model, new antifungal, pulmonary histomorphology, paracoccidioidomycosis.