TITLE: EVALUATION OF THE MECHANISMS OF ACTION OF THE PEPTIDES POLYBIA-MII AND AGELAIA-MPI AGAINST *Cryptococcus neoformans* FUNGUS

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ABSTRACT

Cryptococcus neoformans is known as the etiologic agent of criptococcosis, a disease that commits especially immunocompromised individuals, causing high morbidity and high mortality. The pharmacological treatments available have shown limited efficiency and most of than show side effects. The antimicrobial peptides (AMP) have shown a wide range of action, including antifungal and immunomodulation abilities, so the aim of this work was evaluate two mastoparans isolated from the crude venom of the swarming wasp. It was determined the minimal inhibitory concentration (MIC) of Polybia-MPII and Agelaia-MPI peptides against *C. neoformans*, after 48 hours of incubation. In order to evaluate the mechanism of action, it was performed a membrane permeability test to propidium iodide and fungal morphology analysis by atomic force microscopy (AFM). Additionally, it was induced the formation of this fungus biofilm and then the fungal cells were challenged with the peptides. The results showed that the MIC of Polybia-MPII and Agelaia-MPI was 25 and 12,5 μM, respectively. The treatment of *C. neoformans* with Polybia-MPII, in the concentrations of 100 and 50 μM, has raised the percentual of permeable cells to propidium in 66% and 36%, respectively. In addition, Agelaia-MPI, in the concentrations of 50 and 25 μM, showed an increase of 54% and 36%, respectively. The AFM analysis showed that the treatment with Polybia-MPII and Agelaia-MPI promoted a reduction of the fungal size and an increment in the membrane roughness. Besides, Polybia-MPII and Agelaia-MPI showed activity against the biofilm in concentrations higher than 400 and 100 μM, respectively. This data indicates that both Polybia-MPII and Agelaia-MPI, exhibit fungicidal activity by attacking *C. neoformans* membranes. Furthermore, they were capable of acting against a fungal resistance mechanism. Considering the limited treatment alternatives for systemic mycosis such as criptococcosis, AMPs are promising as a new therapeutic approach, given their high fungicidal capacity and the absence of reports concerning fungi resistance mechanisms triggering. Therefore, the use of these AMPS may be considered as alternative for the development of new antifungal therapies.

Keywords*:* Antimicrobial peptides, *Cryptococcus neoformans*, Mechanisms of action

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