**Title:** Antiadhesive peptide derived from a phage display library as an alternative to paracoccidioidomycosis treatment.

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*Paracoccidioides* spp. are etiological agents of paracoccidioidomycosis (PCM), systemic mycosis of great importance in Latin America and Brazil. The antifungal arsenal available for PCM treatment is limited and present high toxicity. The search for new agents that innovate the mechanism of action are of outmost importance and urgency for the treatment of PCM and other systemic mycoses. An efficient way of helping to combat infection may be by preventing adhesion of the fungus to host cells, once incapable to adhere, the fungus will be unable to colonize different host tissues, the nutrients acquiring will be difficult, facilitating the host immune system to combat the infection. In this sense, using a peptide phage display library, we identified four peptides that bind with high affinity to *Paracoccidioides* spp., inhibiting up to 64% of the adhesion to pneumocytes and up to 57% the adhesion to different ECM components. The fungicidal activity of the peptides was tested against *P. brasiliensis, P. lutzii* and two other important fungal pathogens *Candida albicans* and *Cryptococcus neoformans* and no fungicidal activity was found. Besides this, the treatment of *Galleria mellonella* with the different peptides prior to infection with *P. brasiliensis* and *P. lutzii* showed increasing up to 64% the survivor of larvae infected with *P. brasiliensis* and up to 60% when infected with *P. lutzii,* being the peptide named as p4 the most active for the two species. The p4 is a six amino acids peptide (VVAGSV), with no cytotoxicity activity against pneumocytes A549 and macrophages Raw 264.7. Using chromatography followed by mass spectrometry, we identified that p4 binds to the *Paracoccidioides* hsp90 protein, a protein evolved in morphological changes and proliferation in this fungus. This peptide is able to modulate the *G. mellonella* immune system increasing the production of haemocytes and using *C. elegans* we observed that the treatment of these larvae with p4 stimulates the expression of the ABF-1, ABF-3, CNC-4, NPL-27 and NPL-31 antimicrobial peptides genes. In murine model, the peptide p4 was able to protect the mice reducing significantly the CFU, showing no significant difference when compared with itraconazole, the treatment control. These findings showed us the importance of this peptide for use in the treatment and prophylaxis of PCM and other mycosis of medical importance.

**Keywords:** *Paracoccidioides spp.*; phage display; antiadhesive peptides.

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