

**TITLE:** ANTIFUNGAL ACTIVITY OF BRAZILIAN RED PROPOLIS IN *Candida* spp. ISOLATED FROM VULVOVAGINAL CANDIDIASIS

**AUTHORS:** ALMEIDA, G. P. S. B.<sup>1</sup>; FONSECA, L. A. V.<sup>1</sup>; SILVA, D. M. W.<sup>1</sup>; MACHADO, J. R. R.<sup>1</sup>; NASCIMENTO, T. G.<sup>1</sup>; MOURA, M. A. B. F.<sup>1</sup>; MARANHÃO, F.C.A.<sup>1</sup>

**INSTITUTION:** 1. UNIVERSIDADE FEDERAL DE ALAGOAS, MACEIÓ - AL (Av. Lourival Melo Mota S/N; Cidade Universitária, *Campus* A. C. Simões Maceió – AL. CEP: 57072-900, BRAZIL)

## **ABSTRACT**

Vulvovaginal candidiasis (VVC), caused by *Candida* species, is recognized as the second most frequent vaginal infection among Brazilian women. Brazilian national health system (SUS/RENAME) recommends for VVC treatment drugs as ketoconazole (KET), fluconazole (FLU), itraconazole (ITR) and nystatin (NYS), but antimicrobial resistance (AMR) for these drugs have been frequently reported in *C. albicans* and *Candida non-albicans*. Brazilian red propolis (BRP) from Alagoas is an important natural product, and this work aimed to evaluate the *in vitro* antifungal activity of this BRP against *Candida* species obtained from patients with VVC from Maceió/Alagoas. Clinical isolates identified by PCR as *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei* (5 of each; total of 25) and their respective ATCC strains were cultured in Sabouraud agar and CHROMagar® *Candida* at 37°C (48h). Antimicrobial susceptibility tests (AST) were performed by disk-diffusion and microdilution methods according to CLSI (M44-A2, M27-A2, M27-S4 e M60) for KET, FLU, ITR, NYS, as well as for BRP crude ethanol extract (EE) and its fractions (hexane, ethyl acetate and chloroform). JASP and IBM®SPSS softwares were applied for statistical analyzes. By disc-diffusion method, all ATCC strains were susceptible to CET and NIS, but there was resistance to ITR and FLU mainly in *C. glabrata* and *C. krusei*, including 19 isolates with ITR/FLU co-resistance confirmed by both methods. Among all isolates, we observed resistance to at least 2 antifungal agents, being 12 isolates resistant to CET/ITR/FLU. BRP (EE and fractions) showed minimal inhibitory concentration (MIC) by microdilution ranged from 15.6 to 250 to  $\mu\text{g}/\text{mL}^{-1}$ , with a high MIC ( $500 \mu\text{g}/\text{m}^{-1}$ ) only for *C. parapsilosis* and *C. krusei* in relation to the hexane and ethanolic fractions, respectively. EE was effective against the majority of isolates, but the acetanolic fraction lower MIC ( $250\text{-}62.5 \mu\text{g}/\text{mL}^{-1}$ ), probably due to a greater concentration of flavonoids (86.1%), whereas the chloroform fraction had homogenous MIC among the reference strains ( $250\mu\text{g}/\text{mL}^{-1}$ ) and we confirmed a low MIC for 6 isolates with R-ITR/FLU profile. These results provide new data on the BRP from Alagoas, attesting the anti-*Candida* activity of different fractions for several species frequently involved in VVC. This important pharmacological potential indicates the need for specific research to evaluate the BRP from Alagoas for use in formulations for vaginal application.

**Keywords:** *Candida*, Vulvovaginal candidiasis, Brazilian red propolis, antimicrobial resistance.

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