TITLE: ANTIFUNGAL SUSCEPTIBILITY PROFILE AND POTENTIAL VIRULENCE-ASSOCIATED ATTRIBUTES IN BRAZILIAN CLINICAL STRAINS OF *CANDIDA GLABRATA* AND *CANDIDA NIVARIENSIS*

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ABSTRACT:
Candida glabrata, Candida nivariensis, and *Candida bracarensis* are opportunistic human fungal pathogens that comprise the *Candida glabrata* species complex. Several virulence-associated attributes are involved in its pathogenesis, host-pathogen interactions, modulation of host immune defenses, and regulation of antifungal drug resistance. This study evaluated the *in vitro* antifungal susceptibility profile to eight antifungal agents, the production of seven hydrolytic enzymes related to fungal virulence, the biofilm formation, and the relationship between these phenotypes in 91 clinical strains of *C. glabrata* and in 01 clinical strain of *C. nivariensis* identified by sequencing of ITS1-5.8S-ITS2 region of the rDNA. Thirteen haplotypes comprising the *C. glabrata* strains and one with the *C. nivariensis* strain were generated after ITS sequencing. All studied strains were susceptible to flucytosine. However, *C. glabrata* strains showed resistance to amphotericin B (9.9%), fluconazole (15.4%), itraconazole (5.5%), caspofungin (8.8%), or micafungin (15.4%). High minimum inhibitory concentrations (MICs) were found for voriconazole and posaconazole. Fluconazole and micafungin resistance was also noted in *C. nivariensis.* Overall, *C. glabrata* clinical strains were good producers of catalase, aspartic protease, esterase, phytase, and hemolysin. However, caseinase and phospholipase *in vitro* activities were not detected. *Candida nivariensis* was excellent producer of aspartic protease, good producer of catalase and phytase, but no *in vitro* activity was detected for the other enzymes tested. *Candida glabrata* and *C. nivariensis* were able to produce biofilm. In general, those biofilms presented low biomass, but high metabolic activity. In *C. glabrata* strains, statistically significant correlations were identified between micafungin MIC and esterase production, between fluconazole and micafungin MIC and hemolytic activity, and between amphotericin B MIC and phytase production. These results contribute to clarify some of the *C. glabrata* mechanisms of pathogenicity. Moreover, the association between some virulence attributes and the regulation of antifungal resistance encourage the development of new therapeutic strategies involving virulence mechanisms as potential targets for effective antifungal drug development for the treatment of *C. glabrata* infections.

Keywords: antifungal, *Candida glabrata*, *Candida nivariensis*, hydrolytic enzymes

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