

Title: MOLECULE ACTIVITY TYROSOL, VANCOMYCIN AND BETA-LACTAM ANTIBIOTICS ON GROWTH *Candida* SPP. RESISTANT DERIVATIVES AZOLES, IN PLANKTONIC FORM AND BIOFILM

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Abstract:

Several reports of in vitro resistance of *Candida* spp. strains to antifungal drugs, in particular the azoles, have been reported. The biofilm production is an important virulence factor and has major clinical implications due to increased resistance to antifungal therapy. Thus, the search for new compounds with antifungal activity is necessary. Some studies have shown the activity of the quorum-sensing molecules farnesol and tyrosol, and beta-lactam and glycopeptides against *Candida* species. Therefore, the aim of this study was to evaluate the effect of the quorum-sensing molecule tyrosol and the antimicrobials vancomycin, meropenem, cefepime and piperacillin-tazobactam, alone or combined with classic antifungals, on the growth of azoles resistant *Candida* spp. strains in the planktonic and biofilm forms. For this, strains of *C. albicans* (n = 10) and *C. tropicalis* (n = 10) were used. The minimum inhibitory concentration (MIC) was determined by the microdilution technique as recommended by the Clinical and Laboratory Standards Institute. Additionally, we investigated the action of the antibacterials and tyrosol on biofilm formation and mature biofilm of *Candida* spp. The MIC's for tyrosol ranged from 2.5 to 5 mM and ranging from 500 to 2,000 mg/mL for antibiotics in both species. Synergistic effect was observed in the association between itraconazole and tyrosol (18/20 strains) and between fluconazole and tyrosol (18/20 strains), while amphotericin B and tyrosol combination showed synergism in 5 *C. tropicalis* strains and in 6 *C. albicans* strains. Tyrosol alone showed effect on biofilm formation of both species at 50XMIC concentration ($P < 0.0001$). Regarding the effect of tyrosol on mature biofilm, it was observed an increase in production at 10XMIC and a decrease in production at 50XMIC. The combination of tyrosol and antifungal drugs showed an increase in the mature biofilm directly proportional to the concentration when tyrosol was associated with azoles and a decrease in the mature biofilm when combined with amphotericin B. All antibacterial showed statistically significant effect on biofilm formation of *Candida* spp. ($P < 0.0001$). Regarding the effect of the antibiotics vancomycin, meropenem, piperacillin/tazobactam, and cefepime on the mature biofilm of *Candida* spp., significant reductions in cellular activity at the concentrations MIC/10 ($P < 0.0001$), MIC ($P < 0.0001$), 10XMIC ($P < 0.0001$) and 50XMIC ($P < 0.0001$) were observed. This study presents a possible action of antibacterial and tyrosol, alone or in combination with antifungal drugs, on *Candida* spp. in planktonic and biofilm forms.

Keywords: *Candida* spp.; susceptibility; biofilm; tyrosol; antibacterials.