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## In vitro synergism between berberine and miconazole against planktonic and biofilm Candida cultures.

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### Abstract

**OBJECTIVES:** To investigate the antimycotic activity of the plant alkaloid berberine (BBR), alone and in combination with antifungal azoles, against planktonic and biofilm *Candida* cultures.

**DESIGN:** The minimum inhibitory concentrations (MICs) of BBR, miconazole (MCZ), and fluconazole (FLC) towards *Candida albicans*, *Candida glabrata*, *Candida kefyr*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis* were determined by a microdilution method. For *C. albicans*, the synergistic effects of BBR combined with MCZ or FLC were examined in a paper disc agar diffusion assay and checkerboard microdilution assay. The effect of the BBR/MCZ combination was further investigated in a *C. albicans* biofilm formation model with a dual-chamber flow cell. The effect on metabolic activity of biofilm cells was established using 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT)/menadione.

**RESULTS:** Berberine inhibited the growth of various *Candida* species (MICs 0.98-31.25mg/L) in the following order of susceptibility: *C. krusei* > *C. kefyr* > *C. glabrata* > *C. tropicalis* > *C. parapsilosis* and *C. albicans*. Synergism between BBR and MCZ or FLC was observed in the disc diffusion assay as well as in suspension showing an FIC index <0.5 ( $\Sigma$ FIC=0.19). Whilst neither BBR (16 mg/L) nor MCZ (0.8 mg/L) alone significantly inhibited biofilm formation of *C. albicans*, their combination reduced biofilm formation by >91% after 24 h, as established from the reduction in surface area coverage ( $P<0.01$ ). The BBR/MCZ combination also exhibited synergy against the metabolic activity of pre-formed *C. albicans* biofilms in polystyrene microtiter plates ( $\Sigma$ FIC=0.25).

**CONCLUSION:** Berberine exhibits synergistic effects with commonly used antimycotic drugs against *C. albicans*, either in planktonic or in biofilm growth phases.

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