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Substrates and modulators of the multidrug transporter Cdr1p of Candida albicans in antifungal extracts of medicinal plants.
Kolaczkowski M, Kolaczkowska A, Sroda K, Ramalhete C, Michalak K, Mulhovo S, Ferreira MJ.
Author information
Abstract
The effective treatment of infections caused by the most frequent human fungal pathogens Candida albicans and Candida glabrata is hindered by a limited number of available antifungals and development of resistance. In this study, we identified new extracts of medicinal plants inhibiting the growth of C. glabrata, a species generally showing low sensitivity to azoles. The methanolic extract of Anacardium occidentalis with an MIC of 80 microg ml(-1) proved to be the most active. In contrast to higher azole sensitivity, C. albicans showed increased resistance to several extracts. Investigation of the possible contribution of the multidrug transporter of the ATP-binding cassette superfamily Cdr1p of C. albicans to extract tolerance revealed a differential response upon overproduction of this protein in Saccharaomyces cerevisiae. Whereas the growth inhibitory activity of many extracts was not affected by CDR1 overexpression, increased sensitivity to some of them was observed. In contrast, extracts showing no detectable anticandidal activity including the ethyl acetate extract of Trichilia emetica were detoxified by Cdr1p. The presence of a non-toxic Cdr1p-mediated ketoconazole resistance modulator accompanying growth-inhibitory Cdr1p substrates in this extract was revealed by further fractionation experiments.
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