Molecular mechanisms of action of herbal antifungal alkaloid berberine, in Candida albicans.

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Résumé en anglais	*Candida albicans* causes superficial to systemic infections in immuno-compromised individuals. The concomitant use of fungistatic drugs and the lack of cidal drugs frequently result in strains that could withstand commonly used antifungals, and display multidrug resistance (MDR). In search of novel fungicidals, in this study, we have explored a plant alkaloid berberine (BER) for its antifungal potential. For this, we screened an in-house transcription factor (TF) mutant library of *C. albicans* strains towards their susceptibility to BER. Our screen of TF mutant strains identified a heat shock factor (*HSF1*), which has a central role in thermal adaptation, to be most responsive to BER treatment. Interestingly, *HSF1* mutant was not only highly susceptible to BER but also displayed collateral susceptibility towards drugs targeting cell wall (CW) and ergosterol biosynthesis. Notably, BER treatment alone could affect the CW integrity as was evident from the growth retardation of MAP kinase and calcineurin pathway null mutant strains and transmission electron microscopy. However, unlike BER, *HSF1* effect on CW appeared to be independent of MAP kinase and Calcineurin pathway genes. Additionally, unlike hsf1 null strain, BER treatment of Candida cells resulted in dysfunctional mitochondria, which was evident from its slow growth in non-fermentative carbon source and poor labeling with mitochondrial membrane potential sensitive probe. This phenotype was reinforced with an enhanced ROS levels coinciding with the up-regulated oxidative stress genes in BER-treated cells. Together, our study not only describes the molecular mechanism of BER fungicidal activity but also unravels a new role of evolutionary conserved *HSF1*, in MDR of Candida.
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