Identification of alkaloid compounds arborinine and graveoline from Ruta angustifolia L. Pers for their antifungal potential against isocitrate lyase ICL1 gene of candida albicans

ABSTRACT

Candida albicans has been reported globally as the most widespread pathogenic species contributing candidiasis from superficial to systemic infections in immunocompromised individuals. Their metabolic adaptation depends on glyoxylate cycle to survive in nutrient-limited host. The long term usage of fungistatic drugs and the lack of cidal drugs frequently result in strains that could resist commonly used antifungals and display multidrug resistance (MDR). In search of potential therapeutic intervention and novel fungicidals, we have explored a plant alkaloids, namely arborinine and graveoline for its antifungal potential. Alkaloids belongs to Rutaceae family have been reported with numerous antimicrobial activities. In this study, we aimed to isolate and identify the antifungal active alkaloids of R. angustifolia and assess antifungal effect targeting C. albicans isocitrate lyase (ICL) gene which regulates isocitrate lyase, key enzyme in glyoxylate cycle contributing to the virulence potential of C. albicans. Alkaloids were extracted by bioassay guided isolation technique which further identified by TLC profile and compared with the standard through HPLC and NMR analysis. The antifungal activities of the extracted alkaloids were quantified by means of MIC (Minimum Inhibitory Concentration). The gene expression of the targeted gene upon treatment was analysed using RT-qPCR and western blot. Additionally, this study looked at the drug-likeness and potential toxicity effect of the active alkaloid compounds in silico analysis. Spectroscopic analysis showed that the isolated active alkaloids were characterized as acridone, furoquinoline, 4-quinolone known as arborinine and graveoline. Results showed that each compound significantly inhibited the growth of C. albicans at the dose of 250 to 500 µg/mL which confirm its antifungal activity. Each alkaloid was found to successfully downregulate the expression of both ICL1 gene CaIcl1 protein. Finally, ADMET analysis suggests a good prediction of chemical properties, namely absorption, distribution, metabolism, excretion and toxicity (ADMET) that will contribute in drug discovery and development later on.

Keyword: Anthranillic acid alkaloids; Antifungal; Candida albicans; Ruta angustifolia