LC-MS-Based Metabolomics and Molecular Docking to Characterize *α*-Glucosidase Inhibitors from *Psychotria malayana* Jack Leaves Extract

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Abstract: The plant *Psychotria malayana* Jack belongs to the Rubiaceae family and is locally referred to as "meroyan sakat/salung" in Malaysia. Diabetes has traditionally been treated with *P. malayana* Jack. Despite its potential, scientific evidence for this plant is still lacking. Thus, the current study sought to investigate α-glucosidase inhibitors in *P. malayana* leaf extracts using a metabolomics approach, as well as to illuminate ligand–protein interactions using *in-silico* techniques (molecular docking). The plant leaves were extracted in five different ratios with methanol and water (100, 75, 50, 25 and 0% v/v; water–methanol). After testing for α-glucosidase inhibition activity, each extract was analyzed using liquid chromatography tandem to mass spectrometry. Additionally, the data were subjected to multivariate data analysis by developing an orthogonal partial least squares method in order to establish a correlation between the chemical profile and the bioactivity. The loading plots demonstrated that the m/z signals correspond to the activity of α-glucosidase inhibitors, allowing five putative bioactive compounds to be identified, namely 1-monopalmitin (1), 5′-hydroxymethyl-1′-(1, 2, 3, 9-tetrahydro-pyrrolo (2, 1-*b*) quinazolin-1-yl)-heptan-1′-one (2), *α*-terpinyl-*β*-glucoside (3), machaeridiol-A (4), and 4-hydroxyphenylpyruvic acid (5). The discovered inhibitors were docked against the crystal structure of *Saccharomyces cerevisiae* isomaltase (Protein Data Bank code: 3A4A) using the Auto Dock Vina software. Nine hydrogen bonds were detected in the docked complex, involving several residues, namely ASP352, ARG213, ARG442, GLU277, GLN279, HIE280, HIE351, ASH215, and GLU411. Compound 1, 2, 3, 4, and 5 showed binding affinity values of −6.1, −8.3, −7.6, −10.0, and −6.5 kcal/mol, respectively, indicatied the moderate to good binding affinity of the compounds towards the active site of the enzyme when compared to that of a known *α*-glucosidase inhibitor, quercetin (−8.4 kcal/mol). The five identified compounds showing potential binding affinity towards the *α*-glucosidase enzyme in *in-silico* study, could be the bioactive compounds associated with this plant's traditional use.

Keywords: *Psychotria malayana* Jack; Diabetes mellitus; *α*-glucosidase inhibitors; LC-MS; metabolomics; molecular docking.