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Metabolomics combined with chemometric analysis to identify α-glucosidase inhibitors in *Phaleria macrocarpa* fruit extracts and its molecular docking simulation

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Highlights

- *Phaleria macrocarpa* is widely used as a remedy to reduce blood glucose levels.
- GC–MS is a distinctive method dominating the metabolomics research area.
- Chemometric analysis can be applied to resolve large data sets.

Abstract

Phaleria macrocarpa is a medicinal plant widely available in Malaysia. The plant parts have been traditionally used as an antidiabetic remedy. This study aimed to identify the putative inhibitors of the α-glucosidase enzyme from *P. macrocarpa* using a gas chromatography-mass spectrometry (GC–MS)-based metabolomics approach and further subjected them to *in silico* molecular docking analysis to elucidate the possible mechanism of action. This study assessed the inhibitory potential of *P. macrocarpa* fruit extracts (aqueous, 20 %, 40 %, 60 %, 80 %, and 100 % ethanol) against the α-glucosidase enzyme using GC–MS and chemometric analysis. Orthogonal partial least squares

(OPLS) combined with GC–MS analysis were applied to correlate the inhibition of enzyme activity to the metabolites profile of *P. macrocarpa*. All the potential inhibitors identified were further docked to the yeast (*Saccharomyces cerevisiae*) protein crystal structure (PDB3A4A). The generated score scatter plot of OPLS showed a recognizable separation of all the extracts into six different clusters. GC–MS, incorporated with multivariate data analysis techniques, was used to identify significant chemical markers. Methyl α-D-glucopyranoside, squalene, palmitic acid, myo-inositol and isoquinoline metabolites were identified as putative inhibitors against α-glucosidase activity from *P. macrocarpa*. In conclusion, the GC–MS-based metabolomics approach identified potential chemical markers of *P. macrocarpa* that could be utilized in the development of herbal based medicine.

Introduction

Phaleria macrocarpa (Scheff.) Boerl. is a common herbal plant in Malaysia and Indonesia and widely known as *Mahkota dewa* or God's crown. It has been conventionally used in the treatment of various diseases and disorders. The fruits and leaves are mainly utilized in anticancer treatment, especially against breast cancer and brain tumors. These plant parts are also found to be effective against kidney disorders, liver, heart, and blood-related diseases, hemorrhoids, and stroke. The fruits are also consumed to regulate blood glucose and cholesterol levels. The leaf and seed extracts are reported to be effective as antibacterial and antifungal agents (Altaf et al., 2013). Phytochemical studies of this plant demonstrated various bioactive constituents, such as saponins, tannins, carbohydrates, glycosides, alkaloids, palmitic acid, flavonoids, phenols, polyphenolic terpenoids, lignans, dodecanoic acid, polyphenolic compounds, and ethyl stearate (Easmin et al., 2015). However, reports on the inhibition of *P. macrocarpa* plant parts against α-glucosidase activity incorporated with a bioassay-guided technique are scarce (Sugiwati et al., 2010; Ali et al., 2013).

Comprehensive and systematic phytochemical research should be conducted to investigate the biological activities of the metabolites in *P. macrocarpa*. However, to date, no systematic chemical studies have been performed using this herb. The biological activity of natural products arises from the synergistic effects of the phytochemical composition of complex plant matrixes. Therefore, a comprehensive analytical method should be applied to analyze all existing metabolites in a natural product. Metabolomics is the holistic study of extensive metabolites in herbal products (Salem et al., 2020). Metabolomics techniques combined with multivariate data analysis are increasingly being applied in various chemical and biomedical study areas, such as quality control, chemotaxonomy, biomarker screening, clinical chemistry, environmental metabolism, activity, and toxicity investigation (Li et al., 2022).

Metabolomics research needs robustness, authentic sensitivity, and quantization data from analytical technology. At present, gas chromatography-mass spectrometry (GC–MS), nuclear magnetic resonance (^{1}H NMR) spectroscopy, and liquid chromatography-mass spectrometry (LC-MS) are the distinctive methods dominating the metabolomics research area with wide-ranging characteristics (Emwas et al., 2019). The GC–MS technique is the most desirable metabolomic tool as it is robust and unbiased, with prominent resolution and sensitivity. GC–MS, the easily accessible data from the National Institute of Standards and Technology (NIST), and the Wiley database are used in more research areas, especially for the identification of phytochemical constituents.