UNIVERSITI TEKNOLOGI MARA

METABOLOMICS STUDY OF ASPIRIN-TREATED CARDIOVASCULAR DISEASE (CVD) PATIENTS ALONG WITH AN INVESTIGATION ON ASPIRIN RESISTANCE

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Disease of the heart and blood vessels or cardiovascular disease (CVD) is the leading cause of death worldwide. Prescription of aspirin therapy for its antiplatelet effect has been well documented in the clinical use. However, a phenomenon called 'aspirin resistance' has been reported due to a failure of the aspirin therapeutic effect to protect patients from complications in CVD patients. Although resistance of aspirin has been well determined through the assessment of platelet function, nevertheless its mechanism remains poorly understood. The study of metabolomics in CVD is one of a great potential to assist in the prevention and treatment of the disease through an investigation of the biochemical processes which involves small molecular metabolites. Metabolomics approaches used in this study include profiling of metabolites, analysis of metabolic pathways and discovery of potential biomarkers. A total of ninety-five (95) extracted serum samples were analyzed using high-throughput liquid chromatography mass spectrometry quadrupole time-of-flight (LC/MS Q-TOF). In this study, analyses were performed separately for three (3) cohorts; (i) CVD patients vs. healthy controls; (ii) aspirin resistant vs. aspirin sensitive CVD patients and (iii) matched analysis of CVD patients vs. healthy controls. From the analysis, fatty acid metabolites were highly profiled in the study of the occurrence of CVD. Of interest, metabolites such as 2E,5Z,8Z,11Z,14Z-eicosapentaenoic acid, dihydrosphingosine and purine were considered as the potential biomarker for CVD. These metabolites were found significantly up-regulated in patients. Meanwhile, in the determination of the association of aspirin resistance, metabolites of fatty acids and eicosanoids were among the most highly profiled compounds. Several metabolites were noted as the potential biomarkers of aspirin resistance including 5-S-cysteinyldopamine, butyryl-L-carnitine, 1-methyladenosine, capryloylglycine and tryptophan. Lipid and amino acid metabolism were recognized as the related metabolic pathways involved in the occurrence of CVD in this study. Whereas, pathways such as amino acid metabolism, lipid metabolism, fatty acid metabolism and nucleotide metabolism were found in the analysis of aspirin resistance. Of these pathways, trypthophan and arachidonic acid metabolism were highly associated with the phenomenon of aspirin resistance. Overall, this metabolomics study provides significant metabolites perturbations and important metabolic pathways which are involved in the occurrence of CVDs and its association with aspirin resistance. Thus, this approach could be relevant to CVD disease-related studies and further assist in practice of personalized medicine. However, this preliminary research study requires further validations and investigations prior of application in clinical setting.

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