

UNIVERSITI TEKNOLOGI MARA

**A METABOLOMICS MODEL TO
PREDICT THE CARDIOVASCULAR
DISORDER AMONG THE ORANG
ASLI**

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of the requirements for the degree of
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AUTHOR'S DECLARATION

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

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

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ABSTRACT

Introduction: Majority of the Orang Asli rely on the traditional healing method and belief in self therapy despite the introduction of modern medicine. There are lack of medical or clinical reports on their health status as access to the Orang Asli for medical check up is limited due to the low level of trust and misbelief in the modern medicine. Moreover, routine multiple blood sampling for biochemistry tests are difficult to be conducted among them. Metabolomics has been conducted to profile metabolites which are useful to represent the phenotypes of different disease types and stages. The use of global and targeted metabolomics approach enable us to give an information of their metabolism state and therefore provide the insights to their health status. Hence, it was chosen in this study to predict the phenotype of the self claimed healthy Orang Asli. **Method:** Serum of 83 Orang Asli (OA), 50 healthy volunteers (HT) and 31 patients with history of myocardial infarction (MI) were analysed using LC/MS-Q/TOF. Targeted MS/MS were performed to validate the features of metabolites. Biochemical profiles were determined and recorded for all subjects. Metabolites that were significantly different between MI and HT ($p < 0.005$, > 2 -fold-changes) were validated using AUROC analysis. Metabolites with $AUC > 0.7$ were selected as putative biomarkers, which were further used as variables in building a prediction model (PLSDA) differentiating healthy phenotype and MI. **Results and discussions:** Our finding revealed that lipids were the major metabolites that significantly different between OA and HT ($p < 0.005$). AUROC analysis had identified twenty-two (22) metabolites as potential biomarkers for myocardial infarction. They include 15(S)-HETE ($AUC = 0.997$), phosphorylcholine ($AUC = 0.995$) and 24,24-Difluoro-25-hydroxy-26,27-dimethylvitamin D3 ($AUC = 0.976$). Prediction results revealed that majority of the OA were clustered with the healthy subjects and therefore have similar metabolic state with the group. This shows that they are healthy as they had claimed and as further illustrated by the conventional biochemical analysis. There were however, seven (7) OA whose metabolite profiles were clustered with the patients group, highlighting that they had abnormality in lipid metabolism and implied that they had MI. An evaluation of their biochemistry profiles show abnormalities of cholesterol, triglyceride, HDL and LDL. **Conclusion:** Metabolomics-PLSDA prediction model was developed in this study using comprehensive validation approach and it was able to predict the health status of the Orang Asli. This model was developed using the differential metabolite profiles of the MI and healthy volunteers; and would be useful for categorization of an individual's phenotype to either group.

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CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

1.1.1 Orang Asli and diseases

Orang Asli is known as the 'original people' of Peninsular Malaysia. They have lived in this country for more than hundreds years. They comprise of about 0.5% of the Malaysian population, giving a total of 150 000 (Khor & Shariff, 2008; Mustapha et al., 2010). Most of these people lived in the rural areas such as deep forest, while the minority of them has moved into the urban areas through the resettlement project that was introduced by the Malaysian government (JAKOA, 2010).

The Orang Asli are different from the urban people according to their lifestyle, culture and even nutrition. Healthcare of aboriginal population is poorer compared to populations in the cities all over the world (Booth & Carrol, 2005, Chung et al., 2012). In Malaysia, poverty among the Orang Asli is very high which reaches up to 80% of the Orang Asli population. In addition to this problem, Orang Asli are lack of a better medical treatment, household management as well as good nutrition. Therefore, Orang Asli, especially the children, are prone to disease. As an example, they are prone to infectious disease such as giardiasis, malaria, tuberculosis and leprosy (Hakim et al., 2007; Lim et al., 2009; Othman et al., 2012; Nasr et al., 2013). Other than that, it is also reported that there is an increasing trend of non-communicable disease among these people such as diabetes, asthma, metabolic syndrome, and hypertension (Wan Mohamud and Suraiami, 2010; Ngui et al., 2011; Darwina and Wan Puteh, 2012). Although the prevalence of chronic diseases among the Orang Asli have been reported, the medical information on the disease among them is extremely limited. It is one of the aims in this study to find the possible cause of these diseases among them.