UNIVERSITI TEKNOLOGI MARA

Metabolic response of *Klebsiella pneumoniae* infection in an experimental rat model: Effects of *Moringa oleifera* extract

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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 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

Bacteraemia is defined as the presence of viable bacteria in the bloodstream which can lead to Systemic Inflammatory Response Syndrome (SIRS), multiple organ dysfunction and subsequently death. The pathogenesis of bacteraemia has characteristic features that implied the influence of host's response. Thus, to better understand the metabolic response of the host towards pathogenic infection, a *Klebsiella pneumoniae* infected rat model was developed and investigated using metabolomics approaches. Understanding the pathogenesis better allows the management of the disease better. *K. pneumoniae* was intravenously injected into the rats and serum samples were collected at three different time points (0-hour (pre-infection), 2-hour after infection (early infection) and 192-hour after infection (post-infection) for metabolomics study. Clustering analysis which include Principal Component Analysis (PCA), Partial Least Squares Discriminant Analysis (PLS-DA), Biplot analysis and Hierarchical clustering analysis were used to determine differentially expressed metabolites in response to *K. pneumoniae* infection. Eleven (11) metabolites were characterized as potential biomarkers related to *K. pneumoniae* infection. The potential biomarkers were derived from nine pathways which were found significantly perturbated in the host during *K. pneumoniae* infection. Tryptophan metabolism was the most prominently influenced in *K. pneumoniae*-induced bacteremia according to the metabolic pathway analysis (MetPA). This suggested that significant modulation of the activity of the immune system had occurred during early infection of *K. pneumoniae*. In addition, we also captured several metabolites that indicate the rats were in oxidative stress, inflammation and high energy demand state during early infection of *K pneumoniae*. The involvement of these eleven (11) potential biomarkers in the pathogenesis of bacteraemia were further validated in the sera of the rats pre-treated with *Moringa oleifera* ethanol extract (MOEE). Phytochemical screening of the extract was carried out. Standardization of the extract was done using LCMS Q-TOF and the standardized extract was subjected to acute and repeated dose of 28-day oral toxicity study. Interestingly, most of the potential biomarkers were regulated differentially in the MOEE pre-treatment group when compared to control negative group. Based on the perturbed pathway revealed by the Metabolomics Pathway Analysis (MetPA), oral pre-treatment of MOEE for 14-days, was able to attenuate the effect of *K. pneumoniae* infection towards host through its ability to act as antioxidant and immune booster. This study has successfully identified potential biomarkers and major pathways involved in the *K. pneumoniae* infection. Several biomarkers and their pathways have not been reported previously in relation to infectious disease, thus may provide option for risk stratification and therapeutic modulation for infectious diseases, hence may reduce mobility and mortality due to infection.

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