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**Title** : *IN VIVO* HEPATOPROTECTIVE ACTIVITY OF *Muntingia calabura* LEAVES EXTRACT: A METABOLOMICS ANALYSIS

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*Muntingia calabura* (Muntingiaceae) is known as 'kerukup siam' or 'pokok buah ceri' locally. It has been used in Southeast Asia and tropical America as antipyretic, antiseptic, analgesic, antispasmodic and liver tonic. This study aims to determine the safety and the metabolic pathways involved in the hepatoprotective mechanism of *M. calabura*. Phytochemical analysis of the extract was carried out. The standardization of the extracts was done using LCMS Q-TOF. The standardized extract was subjected to acute and repeated doses of 28-day oral toxicity study. Three different *in-vivo* hepatotoxic models which are $CCl_4$-induced, PCM-induced and alcohol-induced were eveloped and a dose dependent hepatoprotective effect of *M. calabura* (100 mg/kg, 200 mg/kg and 400 mg/kg) was conducted. Body weight, food and water consumption were measured every day and rats were sacrificed to collect the serum samples at the end of the 10-days treatment for $CCl_4$ and PCM induced hepatotoxic rats while samples were collected at the end of 22-days for alcohol-induced hepatotoxic rats. Histopathological study of the liver slice was carried out to confirm the hepatoprotective activity of the extract. Liquid chromatography-mass spectrometry quadrapole time of flight (LC/MS-QTOF) combined with principal component analysis (PCA) were used to determine differentially expressed metabolites due to treatment with hepatoxicant and *M. calabura* extracts. Metabolomics Pathway Analysis (MetPA) was used for analysis and visualization of the pathways involved. This study shows that the body weight, food and water consumption were significantly decreased and histopathological study revealed liver damage in all *in-vivo* models of hepatotoxic rats. PCA score plots of the hepatotoxic rats clustered separately from the control, while groups given pre-treatment with the extract clustered closely with the control. This indicates that the metabolic profiles from the groups which were given pre-treatment with the extract were almost similar to those of the control. Several candidate biomarkers were identified and they were associated with perturbations of major pathways involve in inflammation. Interestingly, all the potential biomarkers were reversed to almost normal level in the group given pre-treatment with the extract. This study has successfully isolated major pathways involved in the hepatoprotective effects of MCME using LCMS Q-TOF metabolomics approach. Several biomarkers and their pathways in hepatoprotection have not been reported previously and may provide potential therapeutic targets and/or options for protection from chemical induced liver injury.