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IMMUNOMODULATORY AND ANTI-INFLAMMATORY POTENTIAL OF *Myrmecodia platytyrea* TUBER AQUEOUS EXTRACT: *IN VIVO* AND *IN VITRO* APPROACHES

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ABSTRACT

Myrmecodia sp. had been traditionally used as a remedy by local people of Papua Island to treat severe diseases such as tuberculosis, hyperuricemia and cancer. Several studies on pharmacological effects of this plant revealed that *Myrmecodia* sp. have potent antioxidant activities, anticancer and antiproliferative activities with immunomodulatory effects. *Myrmecodia platytyrea* was chosen in this study as this plant exhibit a special feature, red hypocotyl, which makes it different from other *Myrmecodia* species. Moreover, very few literatures on this species were found. The main objective of this study was to prove scientifically the effectiveness of this plant in treating diseases as claimed by the ancestors. *M. platytyrea* was extracted using decoction method and phytochemicals in the extract were analysed. *In vitro* toxicity test using MTT assay and *in vivo* oral toxicity test, acute and 28-days repeated dose toxicity test, were done to determine the safety profile of this extract. Further evaluation of *Myrmecodia platytyrea* tuber aqueous extract (MPAE) effects towards immune system and global metabolomics using healthy rats and validated through *in vitro* and *in vivo* study of anti- inflammation of LPS-induced macrophage and carrageenan-induced rat paw oedema. After screening for the phytochemicals in MPAE, the results revealed that MPAE contained flavonoids, phenolics, free-radical scavenging activity and chelating properties. For the cytotoxicity test, MPAE showed $IC_{50}>1000$ μg/mL on normal cell lines after 24 h incubation, which was considered non-toxic. Acute oral toxicity study and 28-days repeated dose toxicity study of MPAE (p.o.), did not cause any toxic effect, physical and behavioral changes to the mice. Immunomodulatory study revealed, MPAE may act as an adjuvant, that signals the immune system to respond to the antigen as it would to an active infection. Next, metabolomics analysis on sub-chronic administration of 400 mg/kg MPAE (p.o.) revealed that MPAE might involve in regulation of fatty acid metabolism, precursors of inflammation, endogenous antioxidant system (GSH) and exogenous metabolites. The results also showed MPAE exhibited anti-inflammatory properties, *in vitro* and *in vivo* by inhibiting the inflammatory biomarkers. Conclusively, MPAE is not toxic, can boost the immune system and inhibit inflammation, may be due to the presence of high phenols and flavonoids content in the extract.

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CHAPTER ONE
INTRODUCTION

1.1 Background of Study

For thousands of years, plants have been a source for medicinal treatments and even today plants-based medicines continue to provide mankind with remedies. Based on surveys by World Health Organization (WHO), about 80% of world's population rely on herbal medicine as primary source of healthcare (Ashafa & Olunu, 2011; Mukinda, 2010). This is because primary health care facilities are unable to manage the number of patients requiring aid, the high cost of Western pharmaceuticals and health care. Therefore, among rural communities of developing countries, the government has encouraged them to use indigenous sources as an alternative medicine to minimize the expenditure on imported drugs (Ashafa & Olunu, 2011). The most common reasons for using herbal medicine are due to the accessibility and affordability in terms of certain cultural elements within the societies. Also, it is corresponding to the patient's belief, concerns on the adverse effects of synthetic medicines and a more personalized health care.

The emergence of new infectious disease, the increase of multidrug resistance in pathogenic microorganisms, the inefficiency due to unwanted side effects of the synthetic drugs and the high cost of bringing to market a single drug have led to the interest in the discovery of the potential drug molecules from medicinal plants (Ahmad et al., 2006; Calver et al., 2010).

According to Willis, (2017), at least 28,187 information on plant species has been recorded as being used medicinally by Kew's Medicinal Plant Names Services (MPNS) but only 4,478 are cited in regulatory publications. In Malaysia, about 2000 of plants species are reported to possess medicinal properties (Bakar et al., 2018). Currently, it is estimated that over 50% of all marketed pharmaceutical medicines derived from plant sources as well as from derivatives of secondary plant metabolites and include aromatic substances, most of which are phenols or their oxygen-substituted derivatives such as tannins (Jamshidi-kia et al., 2018). The first pharmacologically active compound was produced from opium extracted from seed pods of the poppy