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ANTIHYPERTENSIVE MECHANISM OF ETHANOLIC-WATER EXTRACT OF LEAVES OF Ficus Deltoidea var *angustifolia* IN MALE SPONTANEOUSLY HYPERTENSIVE RATS

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AUTHOR'S DECLARATION

I, hereby, 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 result 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.

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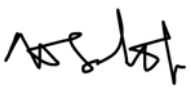
Signature of Student	:	 ……..
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ABSTRACT

The prevalence of hypertension and its associated co-morbidities is increasing in Malaysia. This, despite the availability of modern antihypertensive drugs. Most of these antihypertensive drugs are, however, also associated with side effects, which may influence the patient compliance. There is therefore a need to develop new antihypertensive medications with less or no side-effects to better manage hypertension. *Ficus deltoidea* has recently attracted the attention of scientists for its medicinal value. Although various parts of the *Ficus Deltoidea* plant have been used for centuries in Malay traditional medicine, its effect on blood pressure, however, remains unexplored. This study therefore investigated the blood pressure-lowering effect of standardized ethanolic-water extract of leaves of Ficus deltoidea var *angustifolia* (*FD-A*) in male spontaneously hypertensive rats (SHR). The mechanism of its antihypertensive effect was also investigated. SHR, aged 12-14 weeks, were given daily either 800 mg/kg or 1000 mg/kg of *FD-A* extract of leaves orally for 28 days. Blood pressure was measured weekly using tail-cuff plethysmography and urine was collected using metabolic cages on days 0 and 29. Animals were euthanized on day 29, and serum and tissue samples were collected. Serum and urinary electrolytes, components of the renin-angiotensin-aldosterone-system in serum, serum ET-1, NO and cyclo-oxygenase-2 (COX-2) concentrations, and total antioxidant status (TAC) were measured. ^{1}H-NMR-based metabolomics analysis was performed on the urine. Gene expression analysis was performed on the tissue samples. Liver and kidney functions as well as morphological features of kidney, aorta and liver were also assessed. Compared to the control SHR, blood pressure was significantly lower in *FD-A* treated rats. Both doses showed significant blood pressure-lowering effect as evident from the area under the time versus response curve (AUC). This decrease was comparable to those of Losartan, captopril and aliskerin. Serum concentration of angiotensin I was lower whereas that of ACE was higher in *FD-A* treated rats. *FD-A* treated rats had improved endothelial function as evidenced by lower serum concentrations of ET-1 and eNOS when compared to that in the control SHR. ET-1 gene expression was significantly lower in *FD-A* treated SHR than that in control group. *FD-A* treated rats had higher serum TAC compared to that in the control SHR group. No significant differences were evident in serum COX-2 concentration and serum and urinary electrolytes between *FD-A* treated and control SHR. However, urinary calcium excretion was higher in *FD-A* treated rats. Urine metabolomics study revealed significantly increased excretions of 23 metabolites involved in energy metabolism and antioxidant action in *FD-A* treated rats. Some of these metabolites include hippurate, taurine, dimethylamine, homocysteine, allantoin, methylamine, n-phenylacetylglycine, and guanidinoacetate. Gene expression of FOXO1 was lower whereas the expression of GPx, SOD2 and uricase were significantly higher in the kidney and liver of *FD-A* treated SHR when compared to those in the controls. There were no evident toxic effects of *FD-A* on either the liver or the kidney. In conclusion, ethanolic-water extract of leaves of *FD-A* significantly reduces blood pressure in SHR. The actions of *FD-A* might involve increased TAC and a reduction in ET-1, the latter perhaps reflecting improved endothelial function and redox status in *FD-A* treated rats. These effects also seem to be associated with changes in several metabolic pathways, including taurine and hypotaurine, glycine, serine and threonine, alanine, aspartate and glutamate metabolisms, which require further investigations.

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