INTRODUCTION

Approximately 7.1 million deaths per year may be attributed to hypertension [1] and 1.56 billion people are expected to have hypertension by 2025 (29% of the world’s adult population) [2]. It has been proposed that blood pressure variability is possibly the most important determining factor for this failure [3].

It is recognized that the endothelium is the major determinant of blood pressure at a vascular level and morphological changes occur in endothelial cells in hypertension [4]. Availability of nitric oxide (NO), prostacyclins or endothelium derived hyperpolarizing factor (EDHF) is decreased as well as enhancement of endothelium derived contracting factors (EDCFs) seems to account for endothelial dysfunction in hypertension [5]. Binding of acetylcholine (ACh) to the vascular muscarinic receptors induces the release of NO from endothelial cells [6]. The L-arginine/NO pathway is an important regulatory system in the...
circulation [7] and seems to be involved in the mechanism underlying the antihypertensive effects in spontaneously hypertensive rats (SHRs). It is well known that, there are substances which reduce blood pressure by relaxing vascular smooth muscle [8].

Prostacyclins may play a role in the regulation of blood pressure in normotensive and hypertensive animals [9]. The prostacyclin inhibitor indomethacin is known to block the cyclooxygenase (COX) enzyme [10]. Hence, there are contribution of prostacyclin to endothelium-dependent relaxation of several isolated blood vessels and vasodilatation of perfused organs [11]. It was reported that in stroke-prone SHR [12] and in arteries from diabetic rats [13], COX inhibition augments endothelial dilation and lowers blood pressure. Therefore, both the enzymes and the products of the COX pathway can be altered in hypertension, but it is unclear whether vascular COX activity is increased or decreased in this condition [12].

Treatment with losartan, a selective angiotensin receptor type 1 (AT₁) blocker (ARB), was able to improve endothelial function in aortic rings from spontaneously hypertensive rats [5]. This study also aimed to evaluate the mechanism underlying the effects of AT₁ receptor antagonists on endothelium-dependent and -independent contraction, and endothelium-dependent relaxations in aortic rings of spontaneously hypertensive rats. AT₁ activation leads to initiation of early vascular dysfunction due to the elevation of blood pressure. Besides, overexpression of AT₁ receptor will lead to high blood pressure associated with typical organ complications [14]. Losartan blocks any interaction between angiotensin (Ang) II and its AT₁. Inhibition of AT₁ leads to reduction of heart rate and blood pressure [15] and emphasize the role of AT₁ in hypertension and the needs to complete blockade of its activation [16].

There are seven varieties of Ficus deltoidea; namely var. deltoidea, var. bilobata Corner, var. angustifolia (Miq.) Corner, var. intermedia Corner, var. kunstleri (King) Corner, var. motleyana (Miq.) Corner and var. trengganaensis Corner that were found in the Malay Peninsula [17]. F. deltoidea (mistletoe fig) var. deltoidea, locally known as Mas Cotek, is an alternative therapeutic plant which consists of high content polyphenolic compounds [18] including vitexin that may possess anti-hypertensive effects [19]. It is a medicinal herb and its leaves are enriched with phytoconstituents having various pharmacological activities [20]. F. deltoidea Jack from the family Moraceae [21, 22] traditionally used to treat hypertension [23]. However, there is no scientific report on the antihypertensive mechanism by F. deltoidea. A report issued by the World Health Organization in the year 2000 [24], stated that enhancement activities among modern and traditional medicine will support a clear understanding of the strengths and weaknesses of each, and promote the provision of the best therapeutic option for patients.

This study revealed the vasorelaxant effect of F. deltoidea methanolic and water extract, and the AT₁ on the contribution of the NO and prostacyclin pathways in SHRs using isolated aortic ring.

**MATERIALS AND METHODS**

**Plant and extract preparation**

F. deltoidea leaves extracts (100% methanol, 100% water) were obtained from Department of Chemistry, Universiti Sains Malaysia (USM). The extracts were authenticated by Department of Herbarium in the School of Biological Sciences, USM. A voucher sample of the plant with reference number of 11204 was deposited in the same institute. Methanol extract was obtained by extracting dried and ground leaves of F. deltoidea with methanol using Soxhlet extractor for 17 h and was then dried in vacuum at 40°C; whereas, in the preparation of the water extract, dried ground and crushed leaves were macerated with water at 50°C for 3 hours, and the procedure was repeated twice. Eventually, the extract was filtered and dried in a freeze dryer. Prior to feeding of the animals, both extracts were prepared in distilled water.

**Animals**

Male SHRs weighing 230-280 g were used. The animals were housed in individual cages with supply of food and water ad libitum, and were maintained at the Animal Research and Service Centre (ARASC), Universiti Sains Malaysia, Penang. All procedures involving animals were conducted according to the ethical guidelines by the Animal Ethics Committee, Universiti Sains Malaysia.

**Treatments**

Animals were divided into four groups: vehicle control (SHRN), losartan (10 mg/kg body weight; SHRP), F. deltoidea methanolic extract (1 g/kg BW; SHRM) and F. deltoidea water extract (1 g/kg BW; SHRW). The doses of F. deltoidea methanolic and water extracts were considered safe according to the toxicity study done before [25]. Animals were orally fed daily for 14 days.

**Preparation of isolated thoracic aortic ring [26]**

Following 14 days treatment, rats were anesthetized with sodium pentobarbital (60 mg/kg, ip). The chest and the abdomen were cut opened through a medial sternotomy. The thoracic aorta was carefully isolated, cleaned from the adherent fat and connective tissues, and the aortic tissue was cut into 3-5 mm in length. The
Effects of treatments on the vascular reactivity to phenylephrine

The vascular contraction to PE was evaluated by generating concentration-response curves to PE (10^{-9} to 10^{-3}M) administered as bolus injections of 0.1 ml. The aortic rings either in the presence or absence endothelium were subjected to cumulative concentration-response curves.

Effects of treatments on the vascular reactivity to acetylcholine

Endothelium-dependent relaxation was evaluated using ACh. In this preparation, the tissues were precontracted by PE. Once a plateau line was attained, a concentration-response curve to graded concentrations of ACh (10^{-9} to 10^{-3}M) was generated with each dose of ACh infused for a duration of 4 min. Special care was taken to avoid damaging the luminal surface of the endothelium.

Influence of endogenous nitric oxide on endothelium-dependent vascular reactivity in the phenylephrine-precontraction

Contribution of endogenous NO was evaluated by incubating aortic rings with N^ω-nitro-L-arginine methyl ester (L-NAME; 100 µM as a bolus injection of 0.1 ml), a specific inhibitor of NO synthase, for 30 min prior to precontraction with 0.1 ml PE. Once a maximal contraction to PE was achieved, ACh was added cumulatively to produce a concentration-response curve (10^{-9} to 10^{-3}M as bolus injections, 0.1 ml).

Influence of prostacyclin inhibitor on endothelium-dependent vascular reactivity in the phenylephrine-precontraction

Influence of F. deltoidea extract and losartan on inhibition of prostacyclin inhibitor was evaluated by intravenous administration of a single bolus of indomethacin (100 µM), a specific inhibitor of prostacyclin formation. Isolated aortic rings were exposed to indomethacin for 30 min prior to precontraction with 0.1 ml PE. Once a maximal contraction to PE was achieved, ACh was added cumulatively to produce a concentration-response curve to ACh (10^{-10} to 10^{-5}M as bolus injections of 0.1 ml).

Chemicals

Chemicals of the Krebs-Ringer bicarbonate solution; NaCl and NaHCO₃ from Bendorse Chemicals (Selangor, Malaysia), KCl and KH₂PO₄ from R&M Chemicals (Chennai, India), MgSO₄ from Ajax Chemicals (Sydney, Australia), CaCl₂ and glucose from Systerm®. In addition, losartan potassium was obtained from Merck Sharp & Dohme; PE, ACh, L-NAME and indomethacin from Sigma-Aldrich.

Preparation of drugs

Stock solutions of all drugs were prepared and diluted to the desired concentration with normal saline immediately prior to the experiment except indomethacin, which was dissolved in normal saline containing 5% NaCO₃. Concentrations are expressed as the final molar concentration in the organ chamber.

Statistical analysis

Data are expressed as means ± standard error of the mean (SEM). Concentration-response curve to PE was expressed in grams. The response was considered as the difference between absolute tension and baseline tension. Concentration-responses relationships were evaluated by comparing the overall means of tension achieved. PE-induced dependent and independent contractions were analyzed and comparison between groups was performed by analysis of variance (ANOVA) followed by Bonferroni’s post hoc test using GraphPad PRISM 5 software. The statistical significance of differences between two groups which was the effects of ACh-induced relaxation before and after pre-incubated by L-NAME/indomethacin were analyzed and ascertained by using Student’s two tailed t-test for paired data. A ‘P’ value less than 0.05 was considered statistically significant. In all experiments, ‘n’ equals the number of rats.
RESULTS
Effects of SHRP, SHRM and SHRW on vascular contraction to phenylephrine
PE induced concentration-dependent contractions of the aortic rings in all groups studied in the presence of intact endothelium obtained from spontaneously hypertensive rats (Fig.1). There are significant differences between SHRP and SHRW groups respectively, when compared to SHRN (Table 1). However, in the denuded rings, there was no significant difference in all groups. It shows that removal of endothelium did not affect the concentration dependent contractions in all groups. The tension was significantly higher in the SHRN and SHRM’s intact endothelium compared to denuded endothelium. Maximal contractile response (E\text{max}) in the SHRP and SHRW’s intact endothelium compared to denuded endothelium. Maximal contractile response (E\text{max}) in the SHRP and SHRW’s intact endothelium was significantly developed, but the pD\text{2} value was unaltered. E\text{max} found to be significant in the denuded endothelium of SHRP and SHRM compared to SHRN.

The lowest tension observed in endothelial-intact rings and denuded rings were in SHRW group (E\text{max} = 0.29 ± 0.02) and SHRM group (E\text{max} = 0.23 ± 0.03) respectively. In the SHRW intact aortic rings, pD\text{2} value was similar in SHRN and it was unaltered along with the F.deltoida water extract treatment (Table 1). However, there was no significant difference in the pD\text{2} values between all groups, either in the presence or absence of endothelium.

Effects of SHRP, SHRM and SHRW on vascular relaxations to acetylcholine
To assess the contribution of endothelium-derived relaxation in response to ACh, the aortic rings of SHRs were infused with a graded concentration of ACh. PE induced contraction in intact aorta that relaxed upon addition of ACh, suggesting that the ACh-relaxation was endothelium-dependent (Table 2). Intact endothelium of SHRN, SHRP, SHRM and SHRW were precontracted with PE and then exposed to a series of concentrations of ACh, SHRM and SHRP significantly (P < 0.05) enhanced ACh-induced vascular relaxation as compared to SHRN (R\text{max}: 123.5 ± 13.51; 95.06 ± 8.5 vs 51.87 ± 7.1) (Table 2).

Table 1. The effects of endothelial-intact and denuded aortic rings on the sensitivity (pD\text{2}) and the maximal effect (E\text{max}) of PE-induced contraction in isolated rat aortic ring preparations from spontaneously hypertensive rats in all groups

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Intact</th>
<th>Denude</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E\text{max} (g)</td>
<td>pD\text{2} (log EC\text{50})</td>
</tr>
<tr>
<td>SHRN</td>
<td>0.53 ± 0.03*</td>
<td>7.77 ± 0.33</td>
</tr>
<tr>
<td>SHRP</td>
<td>0.45 ± 0.04*</td>
<td>6.87 ± 0.28</td>
</tr>
<tr>
<td>SHRM</td>
<td>0.3 ± 0.03*#</td>
<td>8.32 ± 0.53</td>
</tr>
<tr>
<td>SHRW</td>
<td>0.29 ± 0.02**</td>
<td>7.87 ± 0.25</td>
</tr>
</tbody>
</table>

Each value represents the means ± SEM; n = 6-12. *P < 0.05 intact vs denude of the same group. \#P < 0.05 between groups compared to SHRN.

Table 2. Values of sensitivity (pD\text{2}) and maximal effect (R\text{max}) of ACh-induced vascular relaxation, in the presence of L-NAME and indomethacin in aortic rings of spontaneously hypertensive rats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Experimental groups</th>
<th>R\text{max} (% relaxation)</th>
<th>pD\text{2} (log EC\text{50})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>SHRN</td>
<td>51.87 ± 7.1</td>
<td>8.45 ± 0.84</td>
</tr>
<tr>
<td></td>
<td>SHRP</td>
<td>95.06 ± 8.5*</td>
<td>7.96 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>SHRM</td>
<td>123.5 ± 13.51*</td>
<td>7.52 ± 0.43</td>
</tr>
<tr>
<td></td>
<td>SHRW</td>
<td>55.23 ± 3.27</td>
<td>8.1 ± 0.29</td>
</tr>
<tr>
<td>L-NAME + Acetylcholine</td>
<td>SHRN</td>
<td>22.27 ± 4.9*</td>
<td>6.32 ± 0.55</td>
</tr>
<tr>
<td></td>
<td>SHRP</td>
<td>24.15 ± 3.2*</td>
<td>6.52 ± 0.36</td>
</tr>
<tr>
<td></td>
<td>SHRM</td>
<td>35.98 ± 7.1*</td>
<td>6.31 ± 0.52</td>
</tr>
<tr>
<td></td>
<td>SHRW</td>
<td>56.52 ± 9.6**</td>
<td>6.01 ± 0.43</td>
</tr>
<tr>
<td>Indomethacin + ACh</td>
<td>SHRN</td>
<td>91.74 ± 2.4</td>
<td>7.33 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>SHRP</td>
<td>90.23 ± 4.9*</td>
<td>7.3 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>SHRM</td>
<td>54.77 ± 6.6*</td>
<td>6.85 ± 0.38</td>
</tr>
<tr>
<td></td>
<td>SHRW</td>
<td>68.83 ± 4.6</td>
<td>7.43 ± 0.23</td>
</tr>
</tbody>
</table>

Values are means ± SEM; n = 6-8. *P < 0.05 absence vs presence of L-NAME; \#P < 0.05 absence vs presence of indomethacin; **P < 0.05 between groups compared to SHRN.
Effects of SHRP, SHRM and SHRW on vascular relaxations to acetylcholine in the presence of L-NAME and indomethacin

To investigate the contribution of NO and COX in endothelium-dependent relaxation, the aortic rings were incubated with L-NAME, a specific inhibitor of NO synthase, and indomethacin, a specific inhibitor of COX. Pre-incubation of the rat aorta rings for 30 min with L-NAME significantly (P < 0.05) inhibits endothelial NOS and attenuates less ACh-induced relaxation in all groups (Fig.2). The maximal response
(R_max) values in the presence of L-NAME showed significant differences only in SHRW as compared to SHRN (R_max = 56.52 ± 9.6 vs 22.27 ± 4.9)(Table 2). In terms of pD2 values, pre-incubation with L-NAME showed no significant difference, even it found to be the lowest pD2 values in SHRW. Pre-incubation of the rat aorta rings for 30 min with indomethacin significantly (P < 0.05) inhibits endothelial COX and attenuated less ACh-induced relaxation in SHRP and SHRM (Fig.3). The R_max in the presence of indomethacin found to be significant only in SHRM and no difference in pD2 values as compared to SHRN (R_max = 54.77 ± 6.6 vs 91.74 ± 2.4)(Table 2).

DISCUSSION

The aim of this study was to investigate the vascular contraction and relaxation effect of F.deltoidea methanolic and water extracts, and the AT1 on the contribution of the NO and COX pathways in SHR. The mechanism of the antihypertensive effects of F.deltoidea leaves is important and there have been studies on endothelium-derived NO (EDNO) [27], the inhibition of EDNO, and inhibition of COX pathway [28]. Since an effect of endothelial function is reported to be the most common [29, 30], we investigated the mechanism of vascular relaxation of F.deltoidea leaves extract by in vitro experiments using rat aortic rings. Results for the in vitro experiments indicated that the vascular relaxation effect of F.deltoidea methanolic leaves extract was abolished by inhibition of L-NAME only but F.deltoidea water extract was abolished by inhibition of L-NAME and indomethacin. Therefore, the mechanism of action of F.deltoidea leaves extract in the vasorelaxant response of rat aortic rings probably works via the NO pathway or both NO/COX pathway.

Our study shows a significant difference in PE-induced contraction in all groups. It shows that in the aortic rings experiments, modulation of the contractile responses by PE, a selective α1-adrenergic receptor agonist occurs in endothelium intact rather than denuded aortic rings. A decreased contractility to PE was detected in SHRN and SHRM by comparing the contraction before and after endothelium removal. It has been suggested that the endothelium-dependent modulator function on vasoconstrictor stimuli is decreased during aging or hypertension [31]. This observation suggests that, due to being denuded, the amount of released NO by the vessel wall is not sufficient at this time to overcome its degradation by superoxide anions. The release of superoxide anions by the blood vessel wall may be due to the presence of neutrophils and macrophages [32]. For α1-adrenoceptor agonists such as PE, the presence of endothelium reduces vascular sensitivity with little change in the maximal response [33]. Meanwhile, SHRP and SHRW shows that after endothelium removal, PE-induced contractions increases and this might be associated with a decreased production of cyclic guanosine monophosphate (cGMP) [34].
The present data also indicate that losartan and both extracts of *F. deltoidea* were able to reduce vascular contractility mediated by $a_1$-adrenergic receptors. The presence of endogenous NO seems to be necessary for the full expression of the effect of losartan and *F. deltoidea* extract on the contractile response to PE in SHR aortic rings. The existence of a crosstalk relationship between $a_1$ and AT$_1$ receptors was also suggested according to the present result of SHRP in PE-induced contraction. Cross talk between AT$_1$ and $a_1$-adrenergic receptors may play an important role in the control of blood pressure in the presence of physiologic regulation in the sympathetic nervous system [35].

The present results show a significant difference between the treatment and concentration response of ACh, which is dependent of endothelium, which in turn cause the relaxation in the aorta of SHR. Antihypertensive treatment with losartan and *F. deltoidea* methanolic extract improved the ACh-induced relaxation and reduced the maximal contractile response to PE in the presence of endothelium. Moreover, aortic rings of SHRM show greater endothelium-dependent relaxation responses to ACh compared to both control, SHRN and SHRP. The relaxant ability of ACh is increased at higher concentrations in SHRM aortic rings; this may be due to release of endothelium-derived vasodilators, impaired transduction mechanism coupling between endothelium smooth muscles or simultaneously release of contracting substances. Meanwhile, the relaxation to ACh was lower in SHRN which could be due to a drop of release/action of EDRF or the release of a prostanoid vasoconstrictor by the endothelium. Furthermore, the vascular endothelium plays an important role in controlling vascular tone via the release of relaxant and contractile factors [36]. ACh-induced relaxation was also reported in the thoracic aorta of SHR [37].

Reduced release of one or more endothelial factors that act as vasodilation such as NO [36], prostacyclin and EDHF [38] may be an explanation for the decreased relaxation in hypertensive rat’s vessel. Despite the fact that NO has been identified as the endogenous nitrovasodilator formed within endothelial cells from L-arginine, there still is some argument whether NO fully or only contribute for endothelium-dependent relaxations. Since EDNO plays an important role in endothelium-dependent relaxation, our first approach was to determine whether EDNO might explain for the ACh-induced relaxation with the use of NO synthase inhibitor. The increased availability of NO partially accounts for the increased endothelium-dependent relaxations observed in SHR. The most important mechanism in the reduction in endothelium-dependent responses is a lower release of NO. This study has already demonstrated that NO synthase inhibition was able to block the relaxation induced by ACh in aortic rings in all groups. However, there is some slight result from SHRW that maybe suggesting the involvement of EDHF acting through calcium-activated K$^+$ channels.

Prostacyclin causes relaxation of vascular smooth muscle by activating adenylate cyclase and increasing the production of cyclic adenosine monophosphate (cAMP) [39]. The effect of prostacyclin on the response to ACh was examined by the use of inhibitor of prostacyclin formation, such as indomethacin. Indomethacin successful inhibits the ACh-induced relaxation in SHRP and SHRM. However, in SHRN and SHRW, the COX-relaxant products might not involve in the relaxation of ACh in the aorta rings which is indomethacin did not modify the ACh-induced relaxation. In most blood vessels, the contribution of prostacyclin to endothelium-dependent relaxation is insignificant, and its effect is potentiated by NO [40]. In endothelium-intact aortic rings, there are some possible contributions of the variable EDRFs such as NO, endothelin-1 (ET-1), prostacyclin, EDHF in reducing the ACh-induced relaxation in the SHR. Furthermore, there are reports that endothelium-dependent relaxations caused by ET-1 [41]. In aorta rings of SHR, it stated that the endothelium-dependent relaxations to ACh are decreasing because of the release of endoperoxides, which is intermediate in the formation of prostacyclins on the vascular smooth muscle cells [42].

Losartan, the first of this new class of drug, is a selective and competitive AT$_1$ receptor blocker [43]. ARB’s treatment will give protection to the vascular resistance of subcutaneous arteries and may reflect improvements in the remodelling of coronary, renal, and cerebral vessels, which could lead to improved outcome for these models [44]. Removal of aortic ring’s endothelium also eliminated the reduction in the PE-induced contraction evoked by losartan in SHRP. It should be noted that the mechanism underlying the reduction in the PE-induced tone exerted by losartan should not be through partial $a_1$-adrenoceptor antagonism because it has been reported that losartan did not present $a_1$-antagonist activity [45]. All this mechanism linked to AT$_1$ receptors, could have contributed to the antihypertensive effects of prolonged treatment in SHRs. This perception is supported by the fact that losartan was able to ameliorate ACh-relaxation in SHR, and further study suggests that inhibition of the mechanisms depending on AT$_1$ receptor activation are related to the observed beneficial vascular effects. In the presence of losartan, it is attributed to the blocking of any interaction between Ang II and its AT$_1$ receptors [46]. By blocking the action of angiotensin, losartan relaxes muscle cells and dilates blood vessels thereby
reducing blood pressure [47]. This suggests that losartan might lower blood pressure through additional mechanisms distinct from Ang II receptor antagonism. The previous study revealed that losartan-induced relaxation was inhibited by L-NAME, telling that the induced response associated with inhibition of AT₁ receptors are at least partly mediated by endothelial NO [48]. The administration of L-NAME reduced the acute blood pressure–lowering effect of losartan in SHR [47]. This indicates that NO could at least partially mediate the short-term hypotensive effect of losartan. Losartan-induced relaxation was inhibited by indomethacin but failed to reduce more ACh-induced relaxation in SHRP. It may be due to the period of losartan administration in the experimental model. Similarly, it has been reported that the losartan-induced relaxation could be due to an enhanced availability of NO and prostacyclin, or of both which could account for the increase in ACh-induced relaxation [15].

The observed improvement in endothelial dysfunction induced by losartan and F. deltoidea extract treatment can be considered as a primary nonspecific benefit that improves the endothelial function [5]. A previous study reported that inhibition of the rat aorta with L-NAME significantly reduced the relaxant effects of the flavonoids against PE-induced contractions. It is suggested that the relaxant effects of F. deltoidea which contains flavonoids [49] may involve the release of NO from the endothelium. The relaxant effects of several groups of flavonoids have been demonstrated to be endothelium-dependent [50, 51] or independent [52]. Our study shows that F. deltoidea improved vascular responsiveness and induced NO-dependent endothelium, which may partly account for its antihypertensive action. It proves that F. deltoidea strongly relaxed thoracic aorta rings pre-contracted with PE. Moreover, the relaxant effect of F. deltoidea was endothelium-dependent and involved activation of NO-synthase. Several medicinal plants, known to possess antihypertensive properties were shown to involve activation of the NO pathway [53]. A number of chemical compounds which are the major constituents of F. deltoidea including tannins, triterpenoids, phenols and flavonoids may account for the observed effects [20, 23]. Based on these reports, we can assume that the antioxidant properties of flavonoids found in F. deltoidea, probably increase the half-life of NO [54], and therefore contribute to the relaxing effect. Interestingly, many studies have demonstrated that flavonoids decrease vascular tone and agonist-induced contraction in isolated rat arteries through stimulation of endogenous NO production from the endothelium [55].

In summary, this study investigated the vasorelaxant effect of F. deltoidea on the vascular reactivity in comparison with losartan, and possible mechanisms involved. Both F. deltoidea extract decreases blood pressure in SHR and this antihypertensive effect is partly due to the vasorelaxant effect which involves NO production by the endothelium. F. deltoidea water extract-induced vasorelaxation was partly mediated via NO-dependent pathway but not the prostacyclin pathway, whereas the F. deltoidea methanolic extract did involve both NO/COX pathway, as did losartan. In addition, F. deltoidea extract was also shown to augment endothelial function. The present study suggests that this natural product may have therapeutic potential in the treatment of cardiovascular diseases, including hypertension. This study may provide a clue to the role of F. deltoidea and more in vivo studies are needed to identify the other mechanisms involved in the vascular activity. It is conceivable that a lot of efforts are still needed not only in the validation of the plants but also in the areas of identifying the active principles in these medicinal plants.

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