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SOME PHARMACOLOGICAL STUDIES OF A HYPOTENSIVE FRACTION FROM *DERRIS SCANDENS*

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ABSTRACT

Bioassay directed fractionation of water extract from dried stems of Derris scandens *Benth. resulted in the isolation of a hypotensive fraction. In the* in vivo *preparation, intravenous injection of the hypotensive fraction (0.04-1.6 mg/kg) caused a decrease in both mean arterial blood pressure and heart rate of anesthetized rats in a dose dependent manner. Pre-treatment of the animals with atropine (1.5 mg/kg, i.v.) did not alter the hypotensive and the negative chronotropic activities of the hypotensive fraction. Pre-treatment of the animal with β-adrenergic receptor antagonist, propranolol (0.6 mg/kg), caused significantly reduced negative chronotropic activities with no change in hypotensive activities of the hypotensive fraction.*

In the in vitro *preparation, the hypotensive fraction caused vasodilatation of endothelium-intact thoracic aortic rings (preconstricted with phenylephrine). This effect was abolished by pre-incubation of blood vessels with N^G-nitro-L-arginine (300 mM), a specific nitric oxide synthase inhibitor, or removing of the vascular endothelium. For the isolated atria, the hypotensive fraction caused a decrease in atrial contraction rate in a dose-dependent manner. In addition, pre-incubation of the atria with the hypotensive fraction (0.1 mg/ml) for 10 min caused lowering in the positive chronotropic effect of the isoproterenol.*

These results suggest that the mechanisms involved for the hypotensive activity of the hypotensive fraction may operate in both ways, a direct effect by inhibiting the β-adrenergic receptor at the atria, and an indirect effect causing the blood vessel to dilate by stimulated release of nitric oxide from the vascular endothelial cells.

INTRODUCTION

Decoction of *Derris scandens* Benth. has been used in Thai folk medicine for many purposes, such as for curing infectious diarrhea and paresthesia[1]. The aerial part is used for a drug promoting long-life, antipyretic, pain-killer and diuretic while the root part is using for killing fish and insects[2]. Dhawan *et al.* (1977)[3]reported that ethanol extract (EtOH:H_2O=1:1) of *Derris scandens* Benth. has abortifacient and antimicrobial activities, while Mokkhasmit *et al.* (1971)[4] found the ethanol extract had hypotensive activity in the dog as well as smooth muscle stimulant on isolated guinea pig ileum. The chemical constituents of the aerial part of the plant have been found to contain lupeol, teraxerol, beta-sitosterol[5] and eturunagarone[6], while the root part contains warangalone (scandenone), chandalone, lonchocarpic acid, scandenin and lonchocarpenin[7,8] which are non-polar compounds. Besides this, Ravanel *et al.* (1984)[9] reported that the root part of all species of the genus *Derris* contain rotenoids which have been used as a fish poison.

However, no studies have yet provided evidence of the pharmacologic activities of the plant on the cardiovascular system. Our preliminary studies using decoction of the plant stem, injected through the jugular vein of nembutal anesthetized rats, showed a marked decrease in blood pressure and heart rate in a dose-dependent manner. A similar result has been found

when using n-butanol fraction which was extracted from the plant decoction. Thus, it is of interest to isolate the hypotensive fraction from the *Derris scandens* Benth. as well as to examine the possible mechanisms involved for the hypotensive activity of the isolated fraction.

MATERIALS AND METHODS

1. Isolation of hypotensive fraction

Stem of *Derris scandens* Benth. was collected from Phang-nga province. Proper identification was made by Prof. Puangpen Sirirugsa, Department of Biology, Faculty of Science, Prince of Songkla University, and the specimen deposited at the Prince of Songkla University Herbarium.

Stem of *Derris scandens* Benth. was chopped into small pieces and air dried. Isolation of the hypotensive fraction followed the scheme in Fig. 1. Dried stem of the plant (1 kg) was simmered in hot water twice (20L x 2) for a three hour period. Clear solution of the two extracts was mixed, simmered at 50 °C to reduced volume to 50 %, and followed by partition extraction with water-saturated n-butanol. The n-butanol phase was collected and evaporated to dryness *in vacuo* and lyophilized. Dried powder (yellow) of the n-butanol fraction was separated by column chromatography followed the method described in Jansakul *et al.* (1987)[10]. The sample was loaded onto the silica column (48 x 500 mm), and eluted with a mixture of ethylacetate and methanol (8:2, V:V), collecting 70 fractions of 50 ml each, which were examined by TLC. Those fractions of similar composition were pooled, evaporated and lyophilized to dryness, yielding four different fractions. The pooled fraction number 3 (Fr.3) contained hypotensive component, which was re-chromatographed on a silica gel column the same manner as above, eluted by gradient concentration (100%-70%, V:V) of chloroform and methanol. Using the same procedure as above, eight different pooled fractions (F3.1 - F3.8) were obtained. The fifth fraction (F3. 5, yield 0.02 % of dried stem) showed pronounced hypotensive activity, which was chosen for further studies in the mechanism involved for the hypotensive effect.

For identification of the hypotensive fraction, each combined fraction obtained from the column chromatography was tested for its hypotensive activity *in vivo* in the rats. The animals were prepared as described in the pharmacological study section below. Each fraction was disolved in saline in a concentration of 10-20 mg/ml and injected through the left jugular vein at the dose of 4-8 mg/kg of animal weight. The pronounced hypotensive and negative chronotropic activities of each fraction was defined when it caused a decrease in mean arterial blood pressure of more than 75 mmHg, and a decrease in heart rate more than 60 beats/min and these activities were prolonged for at least one min.

2. Pharmacological studies of the hypotensive fraction

In vivo preparation

Female Wistar rats in estrus were anesthetized with Nembutal (60 mg/kg). A polyethylene catheter was cannulated through the right common carotid artery and connected to a pressure transducer and polygraph for monitoring blood pressure and heart rate. The animal was then equilibrated for 1 hr. The dose-response relationship to the hypotensive fraction was injected through left jugular vein.

Effects of the hypotensive fraction on blood pressure and heart rates after blocking with atropine or propranolol

After equilibration of animals for 25 min, atropine (1.5 mg/kg) or DL-propranolol (0.6 mg/ml) was injected through the jugular vein. After 20 min re-equilibration, dose- response relationship to intraveneous injection of the hypotensive fraction was investigated.

***In vitro* preparation**

The female rats were killed by cervical dislocation. Both the left and the right atria were excised and mounted immediately in a 20 ml organ bath. For thoracic aorta, two adjacent rings were cut, and the endothelium removed from one by mechanical disruption using the method of Jansakul *et al.* (1989)[11]. The thoracic aortic rings were placed in organ baths and attached to isometric force transducers and the signals recorded on a polygraph. The organ bath contained Kreb's Henseleit solution of the following composition (mM): NaCl 118.3, KCl 4.7, $CaCl_2$ 1.9, $MgSO_4$ $7H_2O$ 0.45, KH_2PO_4 1.18, $NaHCO_3$ 25.0, glucose 11.66, Na_2EDTA 0.024 and ascorbic acid 0.09, maintained at 37°C, and continuously bubbled with 95% O_2 and 5% CO_2.

Prior to addition of drugs, tissues were equilibrated for 60 min under resting tension of 0.5g for atria and 1.0g for thoracic aorta. The Kreb's solution was replaced every 10-20 min.

After equilibration, the presence of functional endothelium of the thoracic aorta was tested as follows. The aortic ring was preconstricted with $3x10^{-6}$ M phenylephrine for 5-8 min (by which time the response had plateaued), and dilator responses to 10^{-6}M acetylcholine recorded. Eighty to ninety per cent vasodilatation to acetylcholine occurred with endothelium-intact rings.

Effects of the hypotensive fraction on thoracic aortae *in vitro*

After 40 min re-equilibration, cumulative dilator response to the hypotensive fraction of the thoracic aortic ring preconstricted with $3x10^{-6}$ M phenylephrine was studied. Follow several washings, only the thoracic aortic rings with endothelium-intact was re-equilibration with N^G-nitro-L-arginine (L-NOARG, $3x10^{-4}$ M) for 30 min, a second cumulative dilator responses to the hypotensive fraction was obtained in the presence of L-NOARG.

Effects of hypotensive fraction on rate and force of isolated atrial contraction *in vitro*

After 40 min equilibration, the cumulative dose-response relationships of the hypotensive fraction on the rate and force of atrial contraction were studied. In a second experiment, cumulative dose-response relationship to isoproterenol was studied. Follow several washings and re-equilibration for 40 min, the atria were then incubated with 0.1 mg/ml of the hypotensive fraction for 10 min, and a second cumulative dose-response relationship to isoproterenol in the presence of the hypotensive fraction was obtained.

Drugs

The following drugs were used: phenylephrine chloride, DL-propranolol, L-NOARG, isoproterenol and acetylcholine chloride were obtained from Sigma, U.S.A.

Statistical analysis

Vasodilator activities by the hypotensive fraction of thoracic aorta were calculated as a percentage of the induced tension which existed at the start of a relaxant concentration-effect experiment.

Other data are expressed as means ± s.e.mean of 4-7 experiments (n=4-7), and tests of

significance made using Student's paired or unpaired t-test or one-way ANOVA. In all cases, a p value of 0.05 or less was considered statistically significant.

RESULTS

As shown in the isolation scheme (Fig. 1) in the first column chromatography, fraction 3 showed pronounced hypotensive activity. Thus, this fraction was re-chromatographed as described previously. Of the eight different fractions separated, only fraction 5 (F 3.5) showed a pronounced hypotensive activity. Thus, fraction 5 was chosen for further studies on the mechanisms involved in the hypotensive effect. Fraction 5 (light yellow powder), however, is not pure. It contains at least three different bands on the TLC-plate (Merck, Darmstadt, Germany, Chromatography solvent: mixture of chloroform : methanol = 8:2, and observe under UV-light), which have rf=0.68, 0.53, and 0.40 for the first, second and third bands, respectively.

The effects of hypotensive fraction on mean arterial blood pressure (MAP) and heart rate(H.R.) are shown in Fig. 2. Basal mean arterial blood pressure and heart rate of anesthetized rats both of control and experimental groups are similar (saline vehicle control group, MAP=149.3±5.6 mmHg, H.R.=401.3±9.4 beats/min, n=4; experiment group, MAP=148.7± 8.1 mmHg, H.R.=417.5±12.0 beats/min, n=7). The hypotensive fraction (0.04-1.6 mg/kg) caused a decrease in mean arterial blood pressure and heart rate in anesthetized rats in a dose-dependent manner, while saline vehicle (0.1 ml) did not have significant effects on blood pressure or heart rate. The lowest dose of the hypotensive fraction (0.04 mg/kg) caused a decrease in blood pressure of about 18.3±15.5 mmHg and a decrease in heart rate to 58.8 ± 7.5 beats/min and the highest dose (1.6 mg/kg) caused decrease in blood pressure of about 97.0 ± 6.9 mmHg and decrease in heart rate to 193.8 ± 37.3 beats/min. There were no signs of acute toxicity such as internal bleeding of liver, lung, gastrointestinal tract or urinary bladder, at any dose of the hypotensive fraction.

The effects of atropine, a non-specific muscarinic receptor antagonist; DL-propranolol, a non specific β-adrenergic receptor antagonist on the lowering mean arterial blood pressure and heart rate by the hypotensive fraction are shown in Fig. 3. Blocking muscarinic receptor by atropine or blocking β-adrenergic receptor by DL-propranolol did not significantly modify the lowering effect of blood pressure by the hypotensive fraction. In the case of heart rate, however, blocking the β-adrenergic receptors by DL-propranolol, caused a diminishing in the lowering of heart rate by the hypotensive fraction

Fig. 4 shows the effects of the hypotensive fraction on the vasodilatation of thoracic aortae in the *in vitro* preparation. The hypotensive fraction caused a dose-dependent vasodilatation of the endothelium-intact thoracic aortic ring which was preconstricted with phenylephrine ($3x10^{-6}$ M). However, the vasodilator activity was abolished by pre-incubation of the endothelium-intact aortic rings with L-NOARG ($3x10^{-4}$ M), a nitric oxide synthase inhibitor or by removal of the vascular endothelium.

The effects of the hypotensive fraction on the rate of contraction of isolated atria, *in vitro* preparation, are shown in Fig. 5. The hypotensive fraction caused a dose-dependent decrease in rate of atrial contraction without any effect on the force of contraction (data not shown). Isoproterenol, a non-specific β-adrenergic receptor agonist, caused a dose-dependent increase in both rate and force of contraction of the isolated atria. Pre-inbubation the atria with the hypotensive fraction (0.1 mg/ml) cause a diminishing in the positive chronotropic effect with no change in the force of atrial contraction produced by the isoproterenol (Fig. 6).

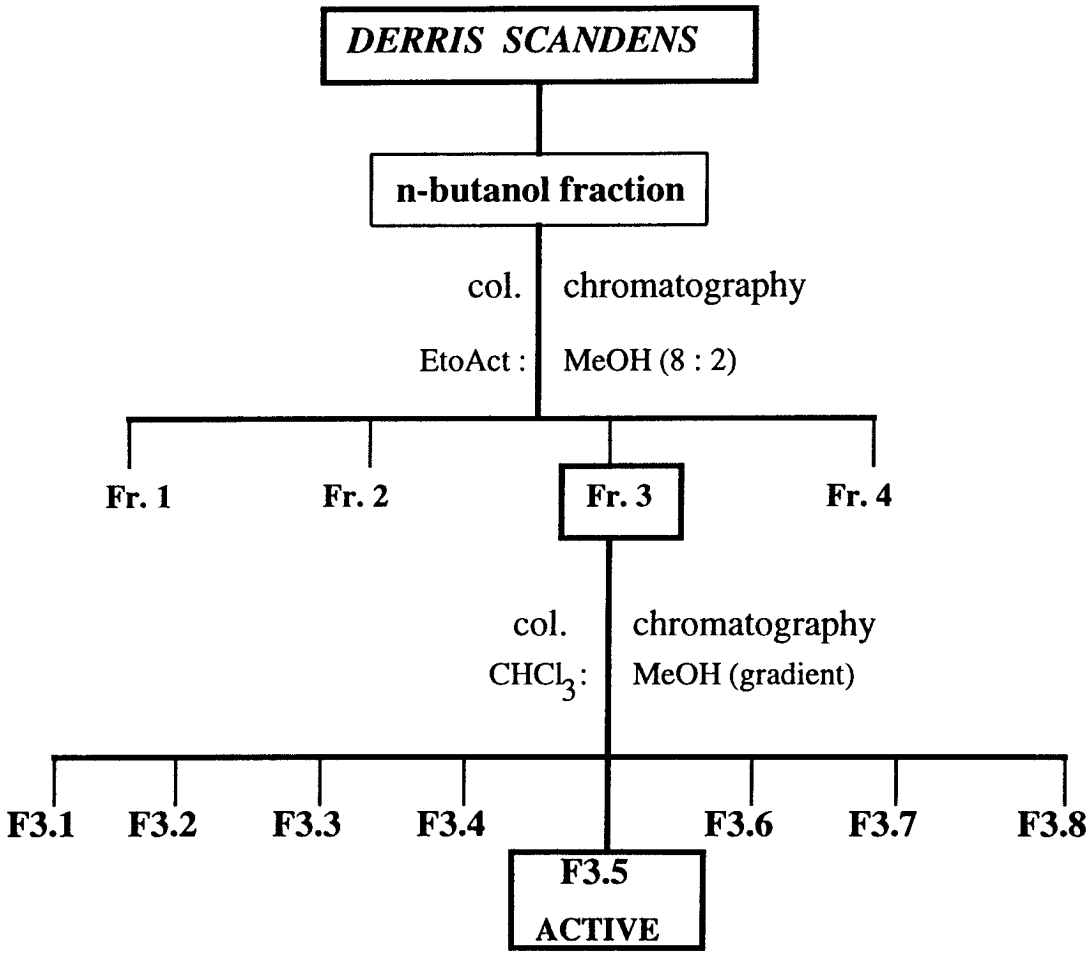

Fig. 1 Isolation scheme of hypotensive fraction from *Derris scandens*.

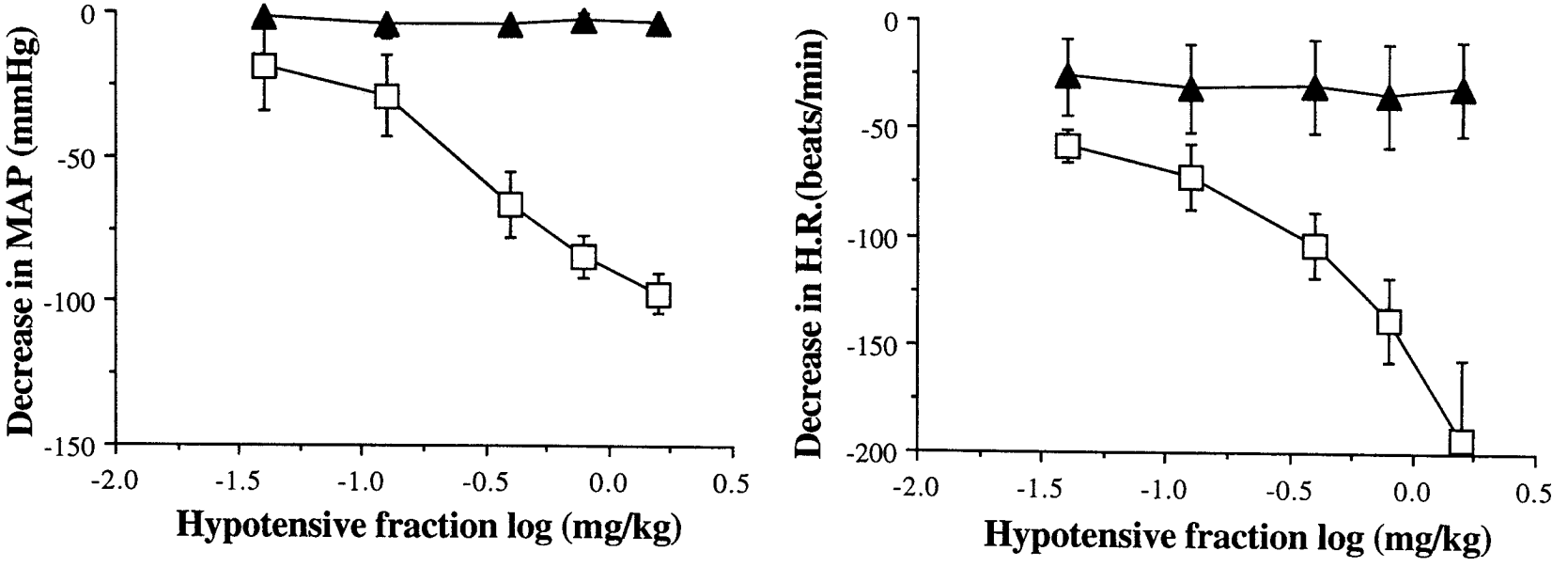

Fig. 2 Effects of hypotensive fraction (❑) on mean arterial blood pressure and heart rate in anesthetized rats compared to those of saline injection (▲). Each point represents the mean ± s.e.mean. of data from 4-7 experiments.

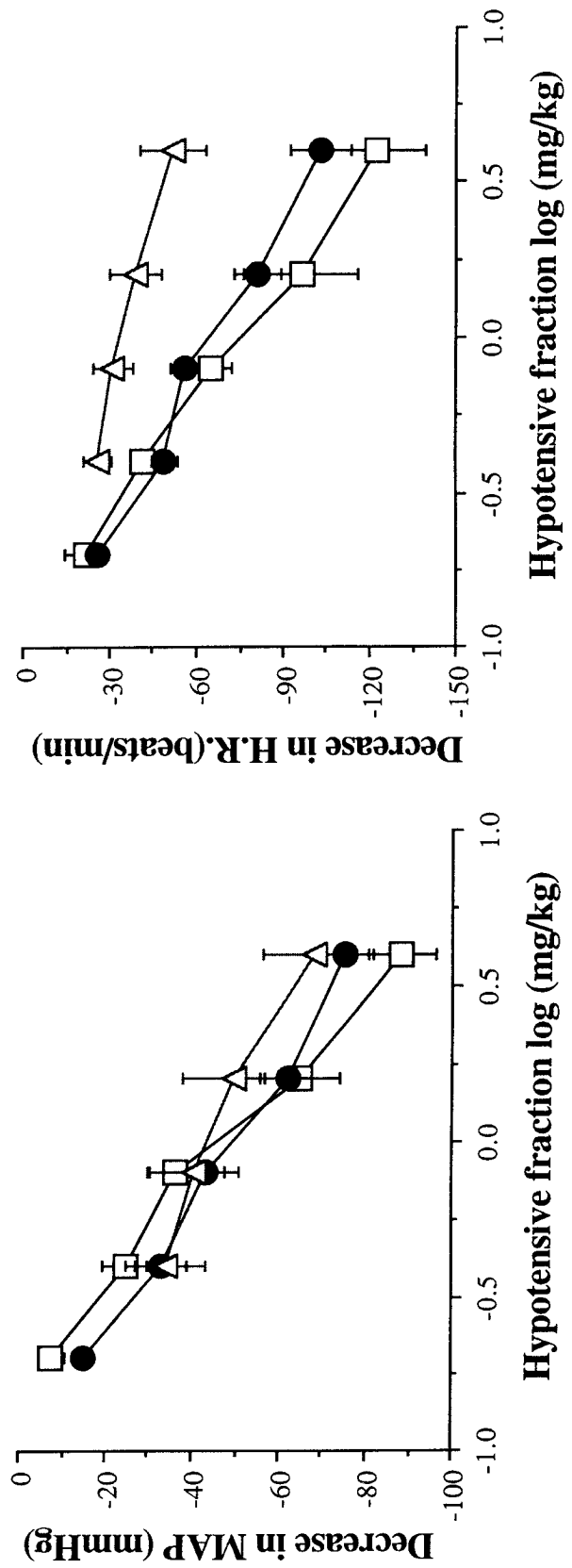

Fig. 3 Effects of atropine and DL-propranolol on the decrease in mean arterial blood pressure and heart rate of the hypotensive fraction in anesthetized rats (□) hypotensive fraction; (●) hypotensive fraction after blocking with atropine; (Δ) hypotensive fraction after blocking with DL-propranolol. Each point represents the mean ± s.e.mean of data from 4-5 experiments.

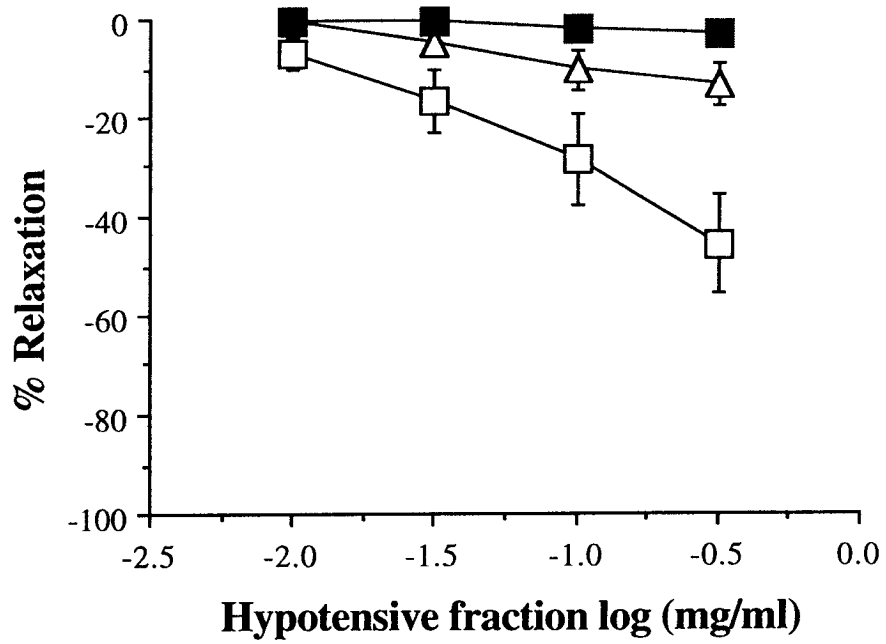

Fig. 4 Effects of hypotensive fraction on vasodilatation of thoracic aorta *in vitro*. (❑) endothelium-intact; (Δ) endothelium-denuded; (■) endothelium-intact in the presence of L-NOARG. Each point represents the mean ± s.e. mean of data from 5 experiments.

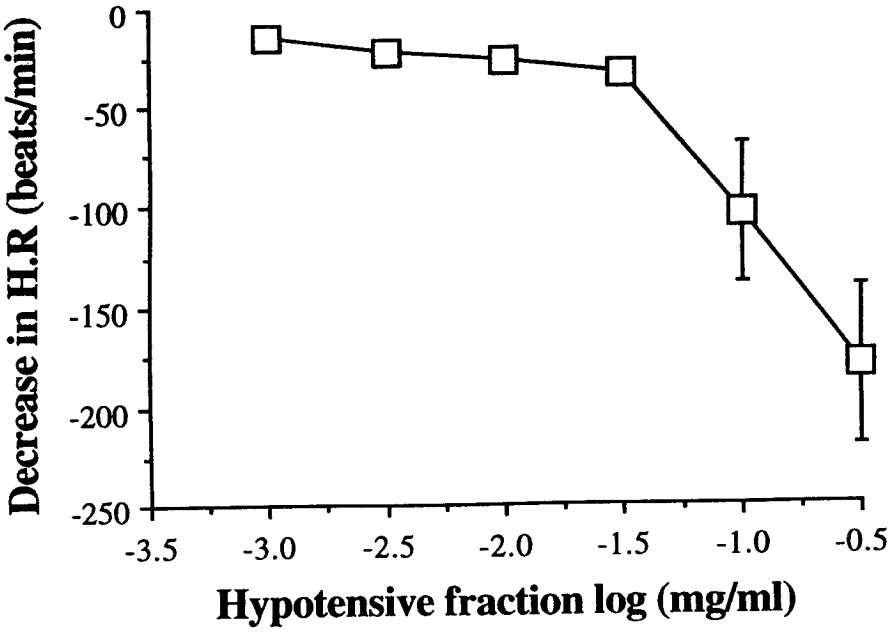

Fig. 5 Effects of hypotensive fraction on atrial contraction rate. Each point represents the mean ± s.e.mean of data from 4 experiments.

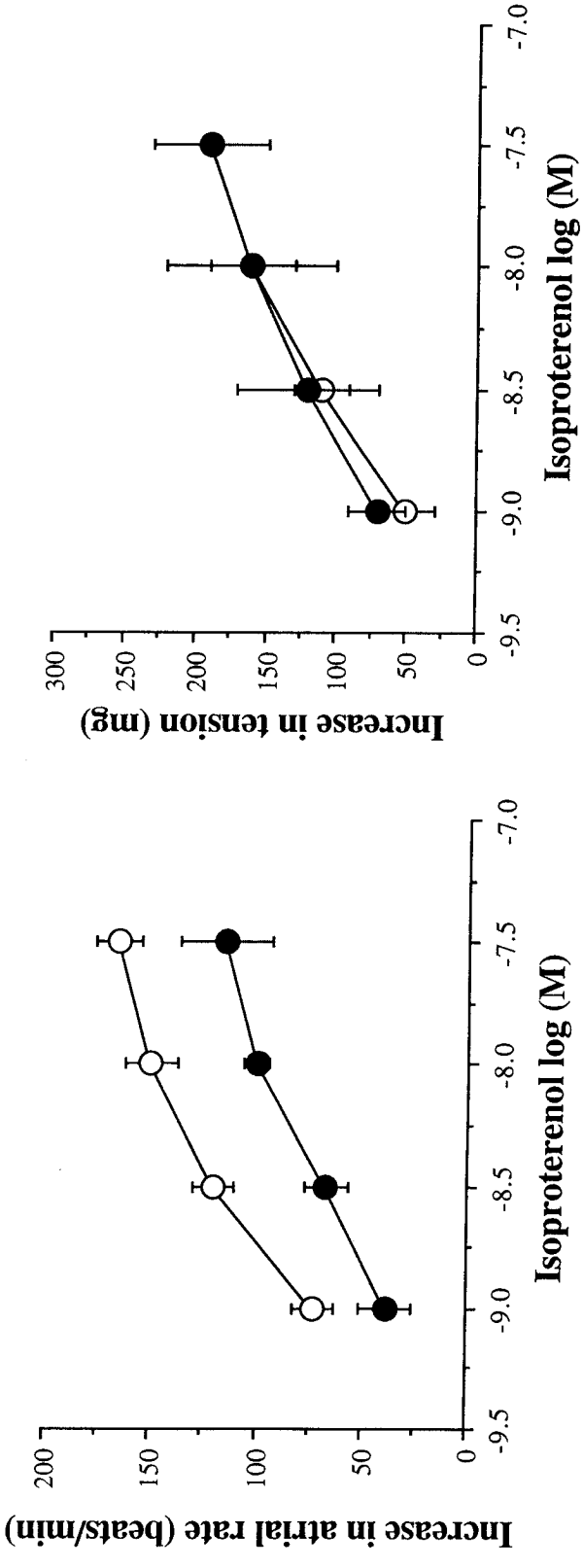

Fig. 6 Effects of hypotensive fraction on the positive chronotropic activity (left) and on force of contraction (right) of isoproterenol on isolated atria. (o) isoproterenol; (●) isoproterenol in the presence of 0.1 mg/ml of hypotensive fraction. Each point represents the mean ± s.e.mean of data from 4 experiments.

DISCUSSION

The hypotensive fraction caused a decrease in both mean arterial blood pressure and heart rate in a dose-dependent manner in anesthetized rats without any signs of acute toxicity. These results are different from those reported by Mokkhasmit *et al.* (1971)[4], who found that the ethanol crude extract of the plant stem caused a decrease in blood pressure, but slightly increase in the heart rate in anesthetized dog. The reason for this may be the crude extract that they used might have contained many different biological substances

Possible mechanisms for the hypotensive and negative chronotropic activities, the drug may act via the muscarinic receptor of parasympathetic nervous system, or behave as a β-adrenergic receptor antagonist of the cardiovascular system. In order to prove the first possibility, the animals were pre-treated with 1.5 mg/kg atropine, a non-specific muscarinic receptor antagonist, about the same dose as reported by Poli *et al.* (1992)[12], for 20 min before studying the dose-response relationship to the hypotensive fraction. As shown in Fig. 3, atropine did not block the hypotensive and negative chronotropic activities of the hypotensive fraction, suggesting that a possible involvement of the hypotensive fraction on muscarinic receptor activation should be ruled out. In order to prove the second possibility, the animals were pre-treated with propranolol (0.6 mg/kg) to block the β-adrenergic receptors of both the blood vessels and the heart. It would be expected that if the hypotensive fraction behaves as the β-adrenergic receptor antagonist, the hypotensive and negative chronotropic activities of the fraction would be diminished. As shown in Fig. 3, pre-treatment the animals with propranolol did not alter the hypotensive activities of the fraction. However, it significantly reduced the decrease in heart rate of the fraction to all doses studied. This indicates that the hypotensive fraction may play a role as a β-adrenergic receptor antagonist of the cardiovascular system.

The hypotensive and negative chronotropic activities of the hypotensive fraction in the *in vivo* of the rats, may act directly at the blood vessels and cause a vasodilatation and/or a decrease in atrial rate or act indirectly through the other systems. In order to prove these possibilities, experiments were performed in the *in vitro* preparation using isolated thoracic aortae and atria. As shown in Fig. 4, hypotensive fraction caused vasodilatation of endothelium-intact thoracic aortic rings preconstricted with phenylephrine, but this effect was abolished by removal of the endothelial cells or by pre-incubation the blood vessels with L-NOARG, a specific endothelial nitric oxide synthase inhibitor.[13] These results suggest the hypotensive fraction has an indirect effect at the blood vessels by stimulating release of nitric oxide from the vascular endothelial cells to cause vasodilatation.[14]

The hypotensive fraction caused a decrease in the rate of atrial contraction in a dose-dependent manner (Fig. 5), with no change on the force of its contraction (data not shown). The results of the *in vivo* experiments suggest that the negative chronotropic effect of the hypotensive fraction may act as a β-adrenergic receptor antagonist at the atria. In order to confirm this possibility, another experiment was done in the isolated atria. Isoproterenol, a β-adrenergic receptor agonist caused an increase in both rate and force of the atrial contraction. Pre-incubation the atria with the hypotensive fraction (0.1 mg/ml) for 10 min, decreased the positive chronotropic effect with no changes in force of atrial contraction produced by the isoproterenol. This suggests that the hypotensive fraction has a β-adrenergic receptor antagonistic effect on the rat atria.

In conclusion, the hypotensive fraction from *Derris scandens* Benth. has hypotensive and negative chronotropic activities in the rat. The mechanisms may involve both a direct effect, as a β-adrenergic receptor antagonist at the atria, and an indirect effect causing the blood

vessels to dilate by stimulating release of nitric oxide from the vascular endothelial cells. However, the hypotensive fraction is a mixture of at least three substances. Therefore, the direct effects and the indirect effects of the hypotensive fraction, may not be of the same compound. Thus, further study by isolation of the pure compound, its chemical structure elucidation, as well as pharmacological studies of each isolated compound will be undertaken to clarify these possibilities.

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บทคัดย่อ

แยกส่วนของสารที่มีผลทำให้ลดความดันโลหิต (hypotensive fraction) จากส่วนสกัดด้วยน้ำจากลำต้นแห้งเถาวัลย์เปรียง โดยวิธีทางเคมี และทดสอบฤทธิ์ของสารด้วยวิธีชีววิธี การศึกษาแบบ *in vivo* ในหนูแร็ทสลบโดยการฉีด hypotensive fraction (0.04-1.6 มก./กก.) เข้าทางหลอดเลือดดำ มีผลทำให้ลดความดันโลหิตและลดอัตราการเต้นของหัวใจ ซึ่งความแรงในการลดความดันโลหิตและการลดอัตราการเต้นของหัวใจแปรผันโดยตรงกับขนาดของสารที่ฉีดให้แก่สัตว์ทดลอง การยับยั้ง cholinergic receptor ด้วย atropine (1.5 มก./กก.) ไม่มีผลทำให้เกิดการเปลี่ยนแปลงความแรงในการลดความดันโลหิตและการลดอัตราการเต้นของหัวใจของ hypotensive fraction แต่อย่างใด การยับยั้ง β-adrenergic receptor ด้วย DL-propranolol (0.6 มก./กก.) ไม่มีผลทำให้เปลี่ยนแปลงความแรงในการลดความดันโลหิต แต่มีผลทำให้การลดอัตราการเต้นของหัวใจโดย hypotensive fraction ลดน้อยลง

การศึกษาแบบ *in vitro* พบว่า hypotensive fraction มีผลทำให้หลอดเลือดแดงทรวงอกที่มีเนื้อเยื่อชั้น endothelium และให้หดตัวอยู่ก่อนแล้วด้วย phenylephrine เกิดการคลายตัว และผลดังกล่าวนี้จะถูกลบล้างไปเมื่อเนื้อเยื่อชั้น endothelium ถูกทำลายหรือโดยการ incubate หลอดเลือดที่มีเนื้อเยื่อชั้น endothelium ด้วย N^G-nitro-L-arginine (300 mM) ผลต่อกล้ามเนื้อ atrium พบว่า hypotensive fraction มีผลยับยั้งการหดตัวได้เองของกล้ามเนื้อ atrium โดยความแรงในการออกฤทธิ์แปรผันโดยตรงกับขนาดของสารที่ใช้ การ incubate กล้ามเนื้อ atrium ด้วย hypotensive fraction (0.1 มก./มล.) นาน 10 นาที มีผลทำให้ลดความแรงในการเพิ่มอัตราการหดตัวได้เองของกล้ามเนื้อ atrium โดย isoproterenol จากผลการทดลองดังกล่าวนี้ชี้ให้เห็นว่า กลไกในการออกฤทธิ์ของ hypotensive fraction ในการลดความดันโลหิตและลดอัตราการเต้นของหัวใจ อาจเกี่ยวข้องทั้งโดยทางตรงโดยมีผลไปยับยั้งที่ β-adrenergic receptor ที่กล้ามเนื้อหัวใจ และโดยทางอ้อมโดยการไปกระตุ้นให้มีการหลั่งของ nitric oxide จาก endothelial cell ของหลอดเลือด แล้ว nitric oxide มีผลทำให้กล้ามเนื้อเรียบของหลอดเลือดคลายตัว