Original Article

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Effects of Ya-hom on cardiovascular functions after long-term oral administration in rats

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Abstract

Ya-hom is one of the most popular Thai traditional medicinal preparations that used for the treatment of dizziness and faintness. Ya-hom is also believed to be efficacious as a mild cardiac stimulant and in improving blood circulation. The present study investigated single oral treatment and long-term oral treatment effect of a selected brand of Ya-hom on cardiovascular functions in rats. Single oral-dose of Ya-hom 2.5-5.0 g/kg increased systolic blood pressure (SBP) and heart rate (HR) in a dose-independent manner. The duration of action of increased SBP and onset of increased HR was dose-dependent. After 8 weeks of daily treatment, both control and Ya-hom-treated groups had 8-10 % elevation in SBP. Increased SBP after single Ya-hom administration was observed only in rats who received the highest dose; the stimulatory effect on HR was not apparent. Increased local plantar blood flow (pBF) was also observed after single oral administration of Ya-hom in a dose-dependent manner. Ya-hom at the highest dose (5.0 g/kg BW) increased the pBF over the duration of 90 min. A similar response of increasing pBF was observed at the end of 8 weeks of Ya-hom treatment. After 8 weeks of Ya-hom treatment at 5 g/kg BW/day, responses to both norepinephrine (NE) and Ya-hom, were greater in the aortic rings of Ya-hom-treated groups than in those of the control group. The stimulating effect of Ya-hom was lower than that of NE. Ya-hom also decreased NE-induced contraction when Ya-hom and NE were simultaneously applied to aortic rings of both control and Ya-hom-treated groups. These results demonstrate that Ya-hom effectuated an elevation in blood pressure, due to stimulatory effects on the large artery and heart. This increase in blood pressure accelerated blood distribution through the microcirculatory system. In long-term use, Ya-hom demonstrated no persistent cardiovascular stimulation, but tended to increase the vascular response to vasoconstrictor. This study confirmed the stimulatory effect of this brand of Ya-hom on cardiovascular functions, in support of its claimed efficacy in the treatment of dizziness and faintness.

Keyword: Ya-hom, blood pressure, heart rate, peripheral blood flow, aortic ring, cardiovascular effects

1. INTRODUCTION

Ya-hom, one of the most popular Thai traditional medicines, is used for the treatment of faintness and dizziness due to its claimed efficacy as a cardiac stimulant and in improving blood circulation. Ya-hom is a multi-medicinal plants formulation that is available under different names and in varying formula compositions. However, most Ya-hom formulae contain similar main ingredient compositions but in differing proportions. Ya-hom continues in frequent and wide spread use, most notably among the elderly. This group tends to consume Ya-hom regularly as a cardiovascular tonic.

Cardiovascular actions of Ya-hom in animals and humans were reported from previous study. In human study, Ya-hom slowed pulse rate and widened pulse pressure[1]. Ingestion of

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3 g of one Ya-hom formula, prepared in both powder and water extract form, increased blood pressure without affecting heart rate[2]. Different extractions of one formula of Ya-hom produced contrary results. Water extract and water-soluble fraction of chloroform extract increased blood pressure; whereas, alcohol extract and water-insoluble fraction of chloroform extract decreased blood pressure, after intravenous injection in rats[1]. Using water extracts of Ya-hom from four brands, data described a blood pressure lowering effect without changing in heart rate[3]. Another report demonstrated that water extract of Ya-hom had a biphasic effect on blood pressure, with an initial transient decrease followed by a long duration of increase, after intravenous administration[4]. One study reported the blood pressure elevating activity of orally ingested Ya-hom[5]. From *in vitro* studies, water extract of three from five brands of Ya-hom formulae showed stimulant effect on force in which two brands had slight depressant effect on rate, of atrial contraction[6,7]. In addition, water extraction of Ya-hom was shown to stimulate isolated aortic ring contraction[7]. Recently, Ya-hom showed *in vitro* antioxidant activity and exhibited inhibitory effect on LDL peroxidation with a half maximal inhibitory concentration equal to 2.43 μg/ml[8].

The effect of Ya-hom on cardiovascular functions in support of its traditional use remains inconclusive. The present study endeavored to investigate the effect of oral ingestion of a selected brand of Ya-hom on cardiovascular functions in rats. Since the effect of long-term use of Ya-hom has never been reported, the effect of Ya-hom on cardiovascular functions after 8 weeks of treatment was also investigated.

2. MATERIALS AND METHODS

2.1. Chemicals

Sodium pentobarbital (Nembutal®) was obtained from Abbot, Chicago, USA Norepinephrine bitartrate was purchased from Sigma Chemical Co., St Louis, USA. Other chemicals were of analytical grade.

2.2. Water extract of Ya-hom preparation

A popular brand of Ya-hom was selected for this study. The Ya-hom powder was purchased from the manufacturer, which is located in Bangkok, Thailand. One hundred grams of Ya-hom contains *Agastache rugosa* (Fisch. et Mey) O. Kuntze (whole plant) 7.1 g, *Acorus Gramineus* Soland (rhizomes) 3.5 g, *Lysimachia foenum graecum* Hance (whole plant) 3.3 g, *Citrus nobilis* Lour (outer yellow ring of the fruit) 7.1 g, *Magnolia officinalis* Rehd et Wils (bark of stem) 11.8 g, *Cinnamomum cassia* Presl (Chinese cinnamon, bark) 7.1 g, *Mentha arventis* L. (Japanese mint, whole plant) 3.5 g, *Asarum sieboldii* Miq (whole plant) 2.3 g, *Ligusticum wallichii* Franch (rhizomes) 9.3 g, *Glycyrrhiza glabra* L. (licorice, rhizomes) 4.8 g, *Eugenia caryophyllata* Thunb (clove, flower-bud) 7.1 g, *Saussuria lappa* Clark (rhizomes) 7.1 g, *Aquilaria agallocha* Roxb (wood) 7.1 g, *Atractylis ovata* Thunb (rhizomes) 9.3 g, Menthol 4.7 g, Borneo camphor 1.4 g, and *Angelica anomala* Lallem (rhizomes) 3.5 g.

Two kg of Ya-hom powder was boiled in 20 L of distilled water for 15 min, and then filtered through a cotton muslin cloth. The filtrate was lyophilized and maintained in airtight containers at -20° C. One gram of Ya-hom powder yielded 0.162 g of lyophilized water extract.

For oral administration, Ya-hom solution was prepared daily by dissolving lyophilized Ya-hom in distilled water, with the concentration expressed as concentration of Ya-hom powder per kilogram of body weight. For isolated aortic ring study, the Ya-hom solution was prepared on the day of experiment by dissolving lyophilized Ya-hom in Krebs-Henseleit (K-H) solution, with the concentration being expressed as concentration of Ya-hom powder in the organ bath (mg/ml).

2.3. Animal

Male Wistar rats, weighing 180-200 g, were purchased from the National Laboratory Animal Center at Salaya Campus, Mahidol University. They were housed in a temperature-controlled (23±2°C) animal room on a 12 h light/dark

cycles, with free access to a normal pellet diet (C.P. Mice Feed; SWT Co., Ltd. Samut Prakan, Thailand), and drinking water. The experimental protocol for this study was approved by the Institute Animal Care and Use Committee of the Faculty of Phamacy, Mahidol University in accordance with Ethical Principles and Guidelines for the Use of Animals for Scientific Purposes, as recommended by the National Research Council of Thailand.

2.4. Determination of blood pressure and heart rate

Systolic blood pressure (SBP, mmHg) and heart rate (HR, beats/min) were simultaneously measured in conscious rats by tail-cuff plethysmography with piezoelectric transducer and indirect blood pressure recorder (Ugo Basile, Varese, Italy).

2.5. Determination of peripheral blood flow

Peripheral blood flow was measured at the left plantar hindpaw skin (pBF, perfusion unit) in rat anesthesized with sodium pentobarbital (50 mg/kg BW; intraperitoneal) using laser doppler flowmetry (LDF) (model DRT4; Moor Instruments, Devon, UK).

2.6. Determination of aortic ring contraction

The thoracic aorta was removed from the anesthetized rat and placed into 37°C K-H solution, which was aerated continuously with 95% O_2 and 5% CO_2. K-H solution is composed of 115 mM NaCl, 4.7 mM KCl, 1.2 mM $MgCl_2$, 1.2 mM KH_2PO_4, 25 mM $NaHCO_3$, 2.5 mM $CaCl_2$, and 10 g/l of glucose. The pH was adjusted to 7.4 with diluted HCl. The 7-mm aortic ring was fastened to a force displacement transducer, which was connected to a polygraph system recorder (Nihon Kohden, Tokyo, Japan). A force of 1 g was applied to the aortic ring and equilibrated for 1 hr before starting the experiment. The force of contraction was continuously recorded until the maximum contraction response was reached, after adding each concentration of NE or Ya-hom. The effect of NE and Ya-hom were studied using the same aortic ring.

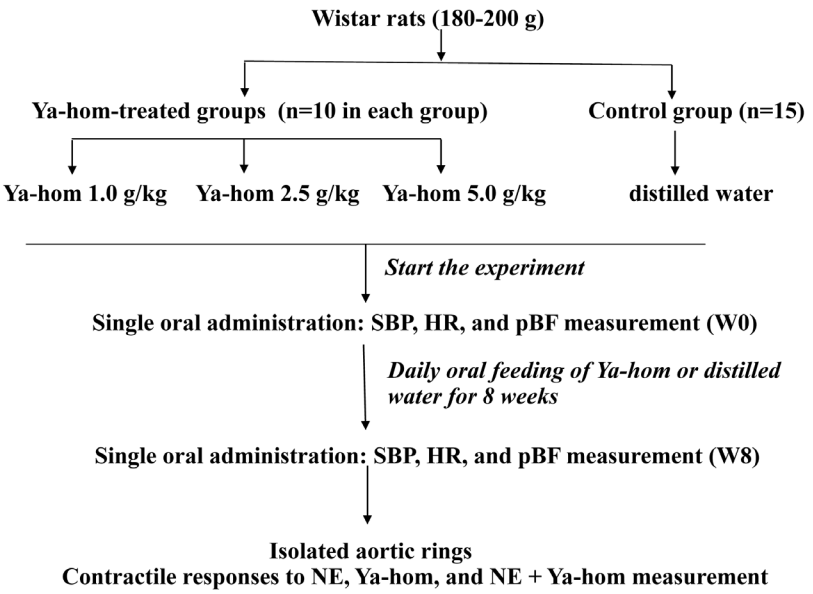

Figure 1. Flow chart of experimental design SBP = systolic blood pressure, HR = heart rate, pBF = plantar blood flow, NE = norepinephrine

Rats were randomly divided into four groups. Three experimental groups received lyophilized Ya-hom, equivalent to 1.0, 2.5, and 5.0 g/kg BW of powder, respectively, and the control group received distilled water. Administration of both Ya-hom and distilled water was by esophageal feeding (Figure 1).

2.7. Effect of Ya-hom on SBP, HR, and pBF

On the first day of the experiment, the change in SBP, HR and pBF after single oral administration of Ya-hom or distilled water were measured before (0 min) and at 15, 30, 45, 60 and 90 min. Then, Ya-hom or distilled water was fed daily for 8 weeks. At the end of the experiment, the effect of single oral administration of Ya-hom or distilled water on SBP, HR and pBF were repeated.

2.8. Effect of Ya-hom on aortic ring contraction

Contractile response to NE (10^{-9}-10^{-5} M) and Ya-hom (1.0-50.0 mg/ml) was investigated in the aortic rings of the Ya-hom-treated group after 8 weeks of daily feeding. The effect of Ya-hom on aortic ring contraction stimulated by NE was also examined by simultaneously adding submaximal doses of Ya-hom and NE.

2.9. Statistical analysis

Data are presented as mean±standard error of the mean (SEM). Differences within group were analyzed by paired t-test (two-tailed) and between 2 groups by unpaired t-test (two-tailed). One-way analysis of variance (ANOVA) was used to compare differences among all groups and Duncan's Student-Newman-Keuls (SNK) test was used to differentiate between statistically significant groups. A *p*-value of less than 0.05 ($p<0.05$) was considered to be statistically significant.

3. RESULTS

3.1. Effect on SBP and HR

3.1.1. The long-term oral dose effect

After 8 weeks of daily treatment, SBP was significantly elevated in control and all Ya-hom-treated groups. However, the increase in SBP was not statistical significantly different between the control and the Ya-hom-treated groups or among the Ya-hom-treated groups. There was no significant change in HR in all groups (Table 1).

Table 1. Systolic blood pressure and heart rate before (W0) and after daily feeding for 8 weeks (W8) of Ya-hom at doses 1.0, 2.5, and 5.0 g/kg BW (Y1, Y2, and Y3) and distilled water (C)

Time	Systolic blood pressure		Heart rate	
	W0	W8	W0	W8
C (n=15)	138 ± 3	149 ± 3*	378 ±5	371 ± 5
Y1 (n=10)	143 ± 4	158 ± 3*	383 ±5	379 ± 5
Y2 (n=10)	139 ± 4	152 ± 5*	388 ±5	376 ± 5
Y3 (n=10)	139 ± 3	151 ± 3*	379 ±5	375 ± 4

Data were expressed as mean ± SEM
*$p < 0.05$: significant difference from the value before daily feeding (W0)
No significant difference among groups in the same week

3.1.2. The single oral dose effect

Before the start of daily Ya-hom treatment, the single administration of Ya-hom at doses 2.5 and 5.0 g/kg significantly increased SBP at 15-30 min and 15-45 min, respectively (Table 2, W0). Similarly, HR significantly increased at 30 min and 15-30 min after administration of Ya-hom at doses of 2.5 and 5.0 g/kg, respectively (Table 3, W0). The highest dose of 5g/kg increased SBP about 13% for 30 min while increased HR about 4% for 15 min.

After Ya-hom daily treatment for 8 weeks, increased SBP after single dose was observed only in 5.0 g/kg Ya-hom-treated group (Table 2, W8). The level of increased SBP was comparable to the response before daily Ya-hom treatment (Table 2, W0 and W8). There was no significant change in HR in response to a single dose of Ya-hom in all groups (Table 3, W8).

Table 2. Changes in systolic blood pressure after single-dose oral administration of Ya-hom at doses 1.0, 2.5, and 5.0 g /kg (Y1, Y2, and Y3) and distilled water (C) in rats before (W0) and after daily feeding for 8 weeks (W8)

Time (min)	Systolic blood pressure (mmHg)							
	Control (*n*=15)		Y1 (n=10)		Y2 (n=10)		Y3 (n=10)	
	W0	W8	W0	W8	W0	W8	W0	W8
0	138 ± 3	149 ± 3	143 ± 4	158 ± 3	139 ± 4	152 ± 3	139 ± 3	151 ± 3
15	138 ± 4	148 ± 4	143 ± 4	158 ± 4	151 ± 2^{*,a}	160 ± 6	152 ± 4^{**,a}	159 ± 6^{*,b}
30	140 ± 3	149 ± 3	141 ± 4	157 ± 7	152 ± 3^{*,a}	159 ± 5	154 ± 3^{**,a}	156 ± 2^{*,b}
45	140 ± 4	150 ± 3	143 ± 4	154 ± 5	149 ± 4	159 ± 5	148 ± 4^{*,a}	157 ± 4^{*,b}
60	140 ± 4	150 ± 3	138 ± 5	156 ± 5	148 ± 4	155 ± 4	143 ± 5	148 ± 3
90	138 ± 3	144 ± 2	142 ± 3	152 ± 3	143 ± 4	151 ± 5	139 ± 3	152 ± 3

Data were expressed as mean ± SEM
*$p < 0.05$, **p < 0.01: significant difference from pre-administration (0 min)
$^{a}p < 0.05$: significant difference from C and Y1 at the same time and in same week
$^{b}p < 0.05$: significant difference from C at the same time and in same week

Table 3. Changes in heart rate after single-dose oral administration of Ya-hom at doses 1.0, 2.5, and 5.0 g /kg (Y1, Y2, and Y3) and distilled water (C) in rats before (W0) and after daily feeding for 8 weeks (W8)

Time (min)	Heart rate (beats/min)							
	Control (*n*=15)		Y1 (n=10)		Y2 (n=10)		Y3 (n=10)	
	W0	W8	W0	W8	W0	W8	W0	W8
0	378 ± 5	371 ± 5	383 ± 5	379 ± 5	388 ± 8	376 ± 5	379 ± 4	375 ± 4
15	380 ± 5	369 ± 5	387 ± 7	382 ± 6	397 ± 7	380 ± 6	387 ± 5*	379 ± 6
30	377 ± 4	367 ± 5	387 ± 6	377 ± 5	396 ± 6^{*,a}	373 ± 6	394 ± 4^{*,a}	376 ± 4
45	382 ± 5	368 ± 4	381 ± 5	373 ± 4	380 ± 6	377 ± 5	381 ± 5	376 ± 4
60	377 ± 6	368 ± 6	384 ± 5	376 ± 5	391 ± 6	371 ± 6	376 ± 4	372 ± 4
90	382 ± 6	367 ± 5	382 ± 5	380 ± 6	384 ± 6	371 ± 6	376 ± 4	371 ± 4

Data were expressed as mean ± SEM
*$p < 0.05$: significant difference from pre-administration (0 min)
$^{a}p < 0.05$: significant difference from C and Y1 at the same time and in same week

3.2. Effect on pBF

Before starting daily Ya-hom treatment, a single administration 2.5 g/kg dose of Ya-hom increased pBF at 30 min. However, a single stimulation 5.0 g/kg dose of Ya-hom increased pBF at 15-90 min, both before and after Ya-hom daily treatment for 8 weeks (Table 4, W0 and W8).

Table 4. Changes in plantar cutaneous blood flow after single-dose oral administration of Ya-hom at doses 1.0, 2.5, and 5.0 g /kg BW (Y1, Y2, and Y3) and distilled water (C) in rats before (W0) and after daily feeding for 8 weeks (W8)

Time (min)	Plantar cutaneous blood flow (perfusion unit)					
	Control (n=15)		Y1 (n=10)	Y2 (n=10)	Y3 (n=10)	
	W0	W8	W0	W0	W0	W8
0	90.8 ± 2.1	91.3 ± 2.8	89.9 ± 4.5	89.6 ± 2.4	86.8 ± 2.1	90.8 ± 2.1
15	90.3 ± 1.9	95.6 ± 2.7	91.8 ± 3.2	93.8 ± 2.9	109.3 ± 3.3^{*,a}	119.0 ± 1.2*,
30	91.4 ± 2.0	93.8 ± 1.9	89.9 ± 3.5	98.7 ± 2.8*	122.7 ± 3.9^{*,a}	122.1 ± 1.3^{*,b}
45	89.7 ± 2.2	91.7 ± 2.1	92.3 ± 6.2	95.7 ± 3.2	113.2 ± 3.6^{*,a}	119.3 ± 1.7^{*,b}
60	88.9 ± 2.1	93.6 ± 5.6	91.9 ± 5.6	89.1 ± 3.3	92.5 ± 2.9*	97.6 ± 2.2*
90	89.6 ± 2.0	91.3 ± 2.6	89.9 ± 4.4	90.6 ± 2.8	89.8 ± 2.0*	95.7 ± 1.9*

Data were expressed as mean ± SEM
$^{*}p < 0.05$: significant difference from pre-administration (0 min)
$^{a}p < 0.05$: significant difference from C, Y1, and Y2 at the same time and in same week
$^{b}p < 0.05$: significant difference from corresponding C at the same time and in same week

3.3. Effect of Ya-hom on aortic ring contraction

NE, a vasoconstrictor neurotransmitter, at a concentration of 10^{-9}-10^{-5} M increased aortic ring contraction to the maximal response of 10^{-5} M in both the control and Ya-hom-treated groups. These responses to NE were significantly greater in the Ya-hom-treated groups than in the control group at every concentration (Figure 2A).

Ya-hom, 1.0-50.0 mg/ml, induced aortic ring contraction with maximal effect at 50.0 mg/ml in both the control and Ya-hom-treated groups. Increased aortic ring contraction in the Ya-hom-treated groups was higher than that of the control at every concentration of Ya-hom, despite there being no statistically significant difference (Figure 2B). Response to stimulation of aortic ring contraction by Ya-hom was less than that of NE. In the presence of Ya-hom 10 mg/ml, aortic ring contraction to NE 10^{-6} M was reduced by 13.8±2.9% and 10.0±1.8% in the control and Ya-hom-treated groups, respectively (Table 5).

Table 5. Effects of NE 10^{-6} M in the absence and presence of Ya-hom 10 mg/ml on the force of contraction of aortic rings from the control and Ya-hom (5 g/kg/day for 8 weeks) treated (Y3) groups

Treatment	Force of contraction (mg)		
	NE	NE + Ya-hom	% decrease
C	558.2 ± 101.1	489.5 ± 92.8*	13.8 ± 2.9
Y3	747.3 ± 102.4	669.5 ± 92.1*	10.0 ± 1.8

Data were expressed as mean ± SEM
$^{*}p < 0.05$: significant difference from NE alone within group
No significant difference between C and Y3 under same conditions

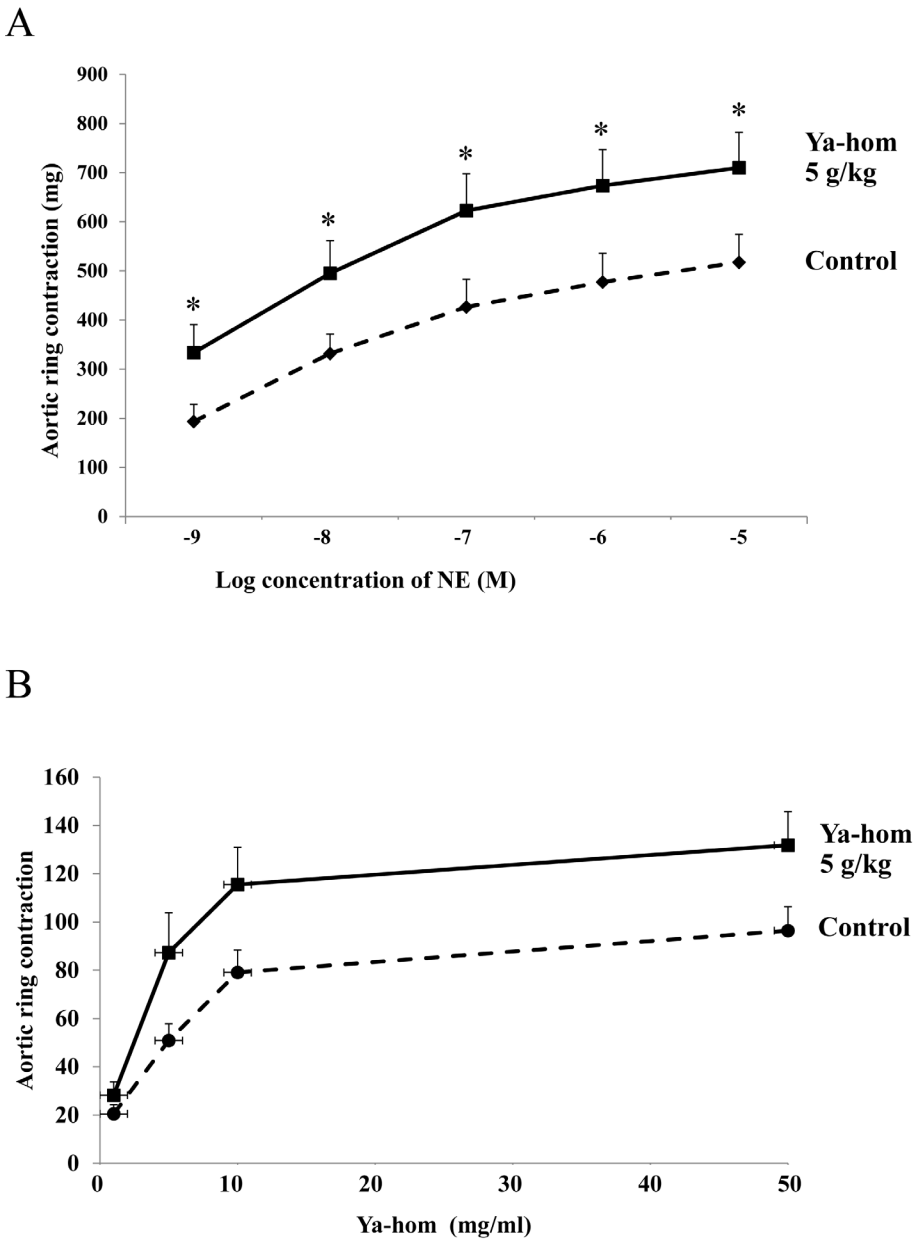

Figure 2. Dose-response of (A) NE, 10^{-9} -10^{-5} M and (B) Ya-hom 1-50 mg/ml, in cumulative addition on aortic ring contraction (mg) from the control and Ya-hom (5 g/kg/day for 8 week) treated rats

*$p < 0.05$: significant difference from the control at the same concentration

4. DISCUSSION

Previous study showed that the dominant effect of Ya-hom was increased blood pressure, although it caused an initial, rapid, and small decrease in blood pressure after intravenous administration at doses 0.6-0.8 g/kg. Times to maximal response and duration of action, but not the increased blood pressure, were dose-dependent[4]. After oral administration of Ya-hom 2-4 g/kg, increased blood pressure was observed. Increased blood pressure and time to maximal response, but not duration of action, were dose

dependent[5]. In the present study, single oral dose of Ya-hom 2.5-5.0 g/kg increased SBP and HR in a dose-independent manner. At the same dose, the percentage and duration of increased SBP was greater than that of HR. It was also noted that duration of action of increased SBP and the onset of increased HR were dose-dependent. Previous studies[6,7] reported the stimulant effect of Ya-hom on force of atrial contraction which was not determined in our study. After 8 weeks of daily treatment, both control and Ya-hom-treated groups had 8-10% elevation in SBP. This indicated that long-term daily ingestion of Ya-hom had no persistent effect on elevation of blood pressure level. However, these rats showed a slight tolerance to a single Ya-hom dose administration. Increased SBP was observed only in rats who received the highest dose (5.0 g/kg) and any stimulatory effect on HR was not apparent.

Increased local pBF was also observed after oral administration of Ya-hom in a dose dependent manner. Ya-hom at the highest dose (5.0 g/kg BW) increased pBF throughout 90 min, with an increase of approximately 34% at 15 min and reaching the maximum effect of 48% at 30 min. The increase in pBF was observed to correspond with the times of SBP and HR elevation, but with higher level and longer duration. A similar increase in pBF was also observed after 8 weeks of Ya-hom treatment. An approximate increase of 20-33% in regional cerebral blood flow within 5 min to 30-45 min was reported after oral administration of Ya-hom 2-4 g/kg. Ya-hom also demonstrated direct vasodilatory effect on cerebral cortex pial arterioles when applied topically[5]. These findings indicated that Ya-hom may increase peripheral blood flow by both indirectly increasing SBP and directly dilating microvessels.

This study also examined the effect of long-term use of Ya-hom on large artery, aortic ring, contraction. Previous study demonstrated that Ya-hom stimulated aortic ring contraction with low potency, when compared to NE. The stimulatory effect of Ya-hom was partly inhibited by phentolamine (α-adrenergic inhibitor), suggesting the partial α-agonist activity of Ya-hom. This was shown by the stimulatory effect of NE being attenuated in the presence of Ya-hom[7]. After 8 weeks of Ya-hom treatment at 5 g/kg BW/day, response to NE was greater in the aortic rings of Ya-hom treated rats than in the control group, at every concentration. Ya-hom showed direct stimulatory effects on aortic ring contraction in a dose-dependent manner, with slightly greater activity in Ya-hom-treated groups than control. This stimulating effect of Ya-hom was lower than that of NE. Ya-hom also decreased NE-induced contraction when they were simultaneously applied to aortic rings from both control and Ya-hom treated groups. These results were similar to the previous study that used aortic rings from normal rats[7] which indicated the partial a-agonist activity of Ya-hom. In addition, the findings from this study suggest the large artery as having increased susceptibility to NE after long-term administration.

This study confirms the stimulatory effect of this brand of Ya-hom on cardiovascular function, supporting the claimed efficacy for treatment of fainting. We demonstrated that Ya-hom causes an elevation in blood pressure as a consequence of stimulatory effects on the large artery and heart. This increase in blood pressure accelerated blood distribution through the microcirculatory system and may have combined with vasodilatation effect on vascular smooth muscle, resulting in increased peripheral blood flow to various organs. In long-term use, Ya-hom showed no persistent cardiovascular stimulation, but demonstrated a propensity to increase vascular response to NE, endogenous vasoconstictor.

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Conflict of interest disclosure

The authors declare no personal or professional conflicts of interest regarding any aspect of this study.

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