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论文题目：The protective effect of huajiaosu in combination with simvastatin on vascular functions in obese rats and its mechanism

Title: The protective effect of huajiaosu in combination with simvastatin on vascular functions in obese rats and its mechanism

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Abstract: Objective: The rate of obesity is increasing yearly. Vascular complications due to obesity are a major factor inducing organ dysfunction. Lowering the blood lipid level is the major treatment against obesity. Simvastatin is a common drug for lowering blood lipid levels, however, its effect on vascular complications is limited. Huajiaosu is a common food seasoning in China. We investigated whether huajiaosu+simvastatin improves vascular functions in obese rats.

Methods and Material: Using a rat obesity model, we investigated the effects of haujiaosu+simvastatin on vascular functions. The aorta vascular elasticity was measured by biological extensometer. The vascular contractile response to norepinephrine and the vascular relaxation response to acetylcholine were measured by a force transducer. Lipid and calcium deposition was investigated by histology, and bone morphogenetic protein 2 (BMP2) and elastin expression was measured by western blotting.

Results: The weight, fat mass, Lee index, blood glucose and lipid levels were significantly increased in obese rats compared with healthy rats. The vascular elasticity and vascular relaxation response decreased, and the vascular contractile response, and lipid and calcium deposition increased in the aorta of obese rats, indicating that the vascular functions were damaged. Simvastatin alone reduced the blood lipid level, weight and fat mass, and slightly alleviated vascular function damage. Huagjiaosu+simvastatin significantly improved vascular functions, as the vascular elasticity and vascular relaxation response were increased, and the vascular contractile response, and lipid and calcium deposition were significantly reduced. We showed that BMP2 and elastin participated in the protective effects of huajiaosu+simvastatin on vascular functions. BMP2 expression was increased and elastin was decreased in obese rats, however, huajiaosu+simvastatin abolished the obesity-induced increase in BMP2 and the decrease in elastin.

Conclusions: Huajiaosu+simvastatin alleviated obesity-induced vascular dysfunction via increasing vascular elasticity and relaxation response, and decreasing vascular lipid and calcium deposition. The mechanism of the huajiaosu+simvastatin effect on

vascular functions is associated with BMP2 and elastin.

Keyword: obesity; vascular elasticity; huajiaosu; simvastatin; rat

目录

报告正文：

1. Introduction

The number of obese individuals in 2016 was higher than that of lean individuals, which threatens human health, with morbidity increasing yearly. There are 432 million obese men and 464 million obese women in China, placing it the first in the world (1). The number of patients with hyperlipidemia is also increasing rapidly, with its morbidity in China reaching greater than 20%, with over 180 million patients (2). Vascular complications induced by obesity and hyperlipidemia are the critical reason for vital organ failure, including heart and renal failure (3,4).

The approaches for preventing cardiovascular complications such as vascular sclerosis induced by metabolic diseases include lowering blood glucose or lipid levels such as statin therapy (5). Despite these advances in treatment, vascular complications remain an enormous problem. Previous studies have found that many foods have protective effects against vascular sclerosis, e.g., red wine and celery (6,7). Huajiaosu is a common food seasoning. It is unclear whether it has protective effects against vascular sclerosis in obesity.

To elucidate this question, we used obese rats to investigate: i. the protective effects of huajiaosu in combination with simvastatin, a blood lipid-lowering drug, against vascular sclerosis; ii. the underlying mechanism of the protective effects of huajiaosu against vascular sclerosis.

2. Materials and Methods

2.1 Ethical approval

The present study was approved by the Research Council and Animal Care and Use Committee of the Research Institute of Surgery, Daping Hospital, Third Military Medical University (Chongqing, China). All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals, published by the US National Institutes of Health (NIH, 2011).

2.2 Animal management

Male and female Sprague–Dawley rats were purchased from the Animal Center of the Research Institute of Surgery, the Third Military Medical University, housed under controlled conditions (22°C, 55%–65% humidity and 12 h light-dark cycle) and fed a standard rat pellet diet.

2.3 Preparation of the obese rat model

The obese rat model was established according to a previous study (8). Six-weeks-old Sprague–Dawley rats were fed a high fat diet, including 77.6% basic forage, 10% yolk, 10% lard oil, 0.2% halo-cholic acid and 0.2% propylsulfur-pyrimidine. After 8 weeks, blood lipid levels were measured. If the rats were at least 20% overweight, with a higher ratio of fat mass/body weight and Lee index, the model was considered successful. The success rate of this model was more than 95% in the present study.

2.4 Experimental protocol and design

The rats were divided into five groups: Control, Obeses, Huajiaosu, Simvastatin and Simvastatin+Huajiaosu. Huajiaosu (3 mg/kg/d) (TianFang medical limited, Henan, China), Simvastatin (20 mg/kg/d) (Merck Sharp & Dohme Limited, Hoddesdon, UK), or a combination of huajiaosu and simvastatin were administrated at the completion of the obesity model to the huajiaosu, simvastatin and simvastatin+huajiaosu groups, respectively. Simvastatin was used to decrease blood lipid levels by inhibiting the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase, thereby decreasing the production of cholesterol, increasing the receptor activity of low density lipoprotein (LDL), and accelerating the decomposition of LDL. Rats in the control and obese groups received no treatment. Eight weeks after administration, the weight, body length, ratio of fat mass/body weight, blood glucose and lipid levels were examined. The aorta was used to examine vascular elasticity, vascular contractile and relaxation responses, expression of bone morphogenetic protein 2 (BMP2) and elastin, and aorta histology (Figure 1).

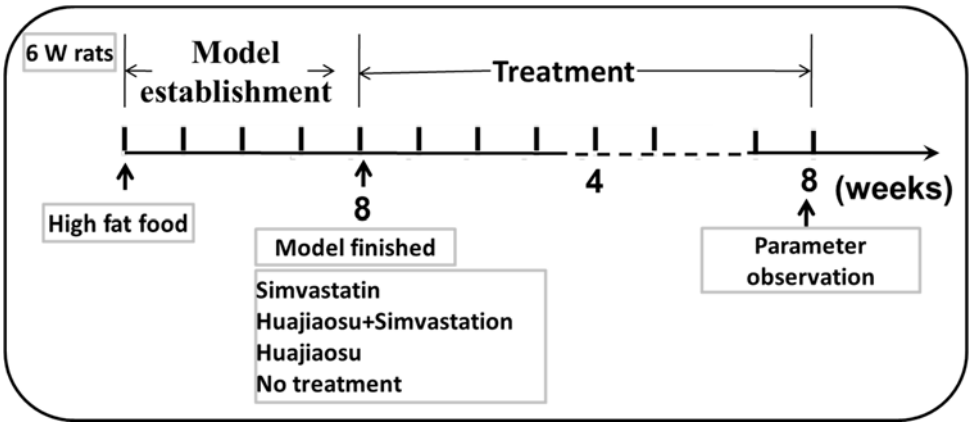

Figure 1. Experiments' timeline. Six-weeks-old rats were fed a high fat diet for 8 weeks, and then the weight and blood lipid levels were measured. The obese rats were given Simvastatin, Huajiaosu+Simvastatin or Huagjiaosu for 8 weeks, after which various parameters were investigated.

2.5 Parameter measurements

2.5.1 Measurements of weight, body length, ratio of fat mass/body weight and Lee index

At 8weeks after drug administration, rats were anesthetized with sodium pentobarbital (30 mg/kg, intraperitoneal). The total amount of sodium pentobarbital was ~50 mg/kg. The weight, body length and mean arterial pressure (MAP) were measured. The Lee index was: Lee index = [weight (g)]$^{1/3}$/body length (cm)*100^3. The mass of the perirenal and epididymal fat were measured (9).

2.5.2 Measurements of blood lipid and glucose levels

Two milliliters of blood were used to measure total cholesterol, triglycerides, LDL, high density lipoprotein (HDL) and blood glucose levels with a Biochemical Analyzer (DX800, Biochemical Analyzer, Beckman, Fullerton, CA, USA).

2.5.3 Vascular elasticity measurement

The aorta was isolated and fixed on a biological extensometer (Tilt meter instrument technology Company limited, Shanghai, China). The length and cross-sectional area were measured. The artery was stretched by the extensometer at 10 mm/min, and the shift and pulling force were recorded. The formula used was: F/S=Y*ΔL/L (F: pulling force; S: cross-sectional area; Y: coefficient of elasticity; ΔL: elongation; L: length of artery) (10).

2.5.4 Measurement of the aorta contractile and relaxation responses

Artery rings were mounted on wire and suspended between a force transducer and a post attached to a micrometer, and then immersed in a 10-mL isolated organ chamber (Scientific Instruments, Barcelona, Spain) containing Krebs-Henseleit solution (in mmol/L): 118 NaCl, 4.7 KCl, 25 $NaHCO_3$, 1.03 KH_2PO_4, 0.45 $MgSO_4$ I $7H_2O$, 2.5 $CaCl_2$ and 11.1 glucose, pH 7.4, which was continuously bubbled with 95% O_2/5% CO_2 and the temperature was maintained at 25°C. The preload was 0.5 g, and the Krebs-Henseleit solution was replaced every 20 min. The tension of the artery rings was determined by a Power Lab System via a force transducer (AD Instruments, Castle Hill, Australia). After 2 h of equilibration, the contractile response of the artery rings to norepinephrine (NE) (1×10^{-9}–1×10^{-4} mol/L) was examined. The relaxation response of the artery rings to acetylcholine (1×10^{-10}–1×10^{-4} mol/L) was also measured (11).

2.5.5 Expression of BMP2 and elastin by western blot analysis

The protein levels of BMP2 and elastin in the aorta were determined by western blotting, as previously described (12). Briefly, the arteries were put into cold protein lysis buffer (pH 7.6, 50 mmol/L Hepes, 150 mmol/L NaCl, 1 mmol/L EDTA, 1% NP-40, 20 mmol/L β-glycerophosphate, 1 mmol/L Na_3VO_4, 1 mmol/L NaF, 1 mmol/L benzamidine, 5 mmol/L para-nitrophenylphosphate, 1 mmol/L DT, and protein kinase inhibitor cocktail tablets) and homogenized on ice. The supernatants were collected, incubated on ice for 1 h, and centrifuged at 8000 × *g* for 10 min at 4°C. The supernatants were collected. The total protein was boiled for 5 min and electrophoresed on a 10% SDS-polyacrylamide gels. The gels were transferred onto PVDF membranes, which were blocked with 10% nonfat dry milk for 1 h and incubated with primary antibodies against BMP2 and elastin (1:1200 and 1:1000, respectively) for 12 h at 4°C. Then, the membranes were further incubated with fluorescent labeling secondary antibodies, and examined by the odyssey CLX infrared imaging system (Gene company limited, USA). The intensity of the immunoreactive bands was quantified and the results were normalized to β-actin levels.

2.5.6 Aorta pathological observations

The aorta was excised from rats, fixed in 4% paraformaldehyde for 3 days, dehydrated through an ethanol gradient and embedded in paraffin at 60°C. Microtome sections of 5 μm thickness were mounted on silanized slides. Subsequently, samples were deparaffinized with xylene, rehydrated, stained with Haematoxylin and eosin, mounted for light microscopy and examined by an experienced pathologist.

2.6 Statistical analyses

Data are presented as the mean ± standard deviation of *n* observations. Statistical differences were analyzed by repeated three-way ANOVA, followed by *post-hoc* Tukey's test (SPSS version 15.0, SPSS Inc., Chicago, IL, USA). $P < 0.05$ (two-tailed) was considered statistically significant.

3. Results

3.1 Effects of huajiaosu+simvastatin on weight, MAP, fat mass and Lee index in obese rats

The criteria for obesity include body weight increasing by at least 20%, and increase in fat mass and Lee index. First we investigated the effect of huajiaosu on body weight, the fat mass of perirenal and epididymal fat, and the Lee index. We found that the body weight gradually increased with age in healthy rats, whereas the weight of the obese rats increased significantly more. Administration of simvastatin, huajiaosu or both decreased the weight of the obese rats, with the combined treatment giving the best results. The changes in Lee index and the fat mass/body weight ratio were similar to the weight changes in every group. The Lee index decreased from 281.56 in the obese group to 247.48 in the Simva+Huajiaosu group; the fat mass of perirenal and epididymal fat decreased from 2.01 g and 7.25 g, respectively, in the obese group to 1.34 g and 5.04 g, respectively, in the Simva+Huajiaosu group. At the end of the obesity model establishment, MAP did not increase compared with the healthy rats, while it significantly increased after another 8 weeks of obesity. Simvastatin, huajiaosu or their combination antagonized the obesity-induced increase in MAP (Table1). The results indicated that simvastatin decreased the body weight, fat mass and Lee index. However, the effects of huajiasu+simvastatin were stronger than simvastatin or huajiaosu alone.

Table 1. Changes in weight, Lee index, fat mass and MAP

Group	Weight, g	Lee index	Fat mass (g)		MAP
			Perirenal	Epididymal	mmHg
Healthy	253.0±8.4	240.32±3.52	1.11±0.03	4.39±0.22	113.5±4.6
Obese	390.0±7.1**	281.56±2.72**	2.01±0.03**	7.25±0.08**	130.3±4.8**
Simva	296.5±7.5#	251.23±3.13##	1.45±0.04##	5.64±0.17##	119.0±3.2#
Huajiaosu+Simva	286.5±7.1	247.48±5.25	1.34±0.02@	5.04±0.18@	112.5±4.9
Huajiaosu	316.4±3.1#	256.88±2.35##	1.85±0.03##	6.32±0.13##	112.3±6.3#

Simva: Simvastatin. ** $P < 0.01$ vs. healthy group; # $P < 0.05$, ##$P < 0.01$ vs. obese group; @ $P < 0.05$ vs. simvastatin group.

3.2 Effects of huajiaosu on blood lipid and glucose levels in obese rats

The blood glucose and blood lipids, cholesterol, triglycerides, HDL and LDL did

not significantly change with age in healthy rats. In obese rats, blood glucose, blood lipids, cholesterol, triglycerides and LDL significantly increased after the model was established, and were significantly higher than in healthy rats. However, HDL was lower in the obese rats compared with the healthy rats. Simvastatin, huajiaosu or their combination significantly decreased serum cholesterol, triglycerides and LDL, compared with the model rats, and the combination treatment gave the best results (Table 2). Furthermore, these treatments increased the HDL level, compared with the obese rats.

Table 2. Changes in blood glucose and lipid levels

Group	Glucose, mmol/L	CHOL, mmol/L	TG, mmol/L	LDL, mmol/L	HDL, mmol/L
Healthy	5.96±0.10	1.17±0.14	0.34±0.03	0.41±0.02	0.89±0.03
Obese	6.57±0.16*	9.72±0.24**	8.53±0.24**	8.45±0.24**	0.56±0.02*
Simva	6.24±0.08	3.23±0.38	2.99±0.10##	4.00±0.07##	0.68±0.03
Huajiaosu +Simva	6.08±0.12	2.93±0.09	2.08±0.12	3.27±0.14	0.86±0.03
Huajiaosu	6.14±0.10	4.39±0.33	4.49±0.30##	4.02±0.15##	0.86±0.05#

Simva: Simvastatin. CHOL: cholesterol; TG: triglyceride; LDL: low density lipoprotein; HDL: high density lipoprotein; * $P < 0.05$, ** $P < 0.01$ vs. healthy group; # $P < 0.05$, ##$P < 0.01$ vs. obese group.

3.3 Effects of huajiaosu on vascular elasticity in obese rats

Vascular sclerosis is a major factor that induces severe complications in metabolic diseases such as diabetes, hyperlipidemia and hypertension. Vascular elasticity is a major parameter that reflects vascular sclerosis (13). We found that the vascular elasticity in the obese rats was significantly decreased and that the coefficient of elasticity increased. Simvastatin or huajiaosu administration alone slightly improved the vascular elasticity, while their combination significantly improved it. The coefficient of elasticity was 4.9 in the obese group and 2.1 in the combination group ($P < 0.01$; Figure 2).

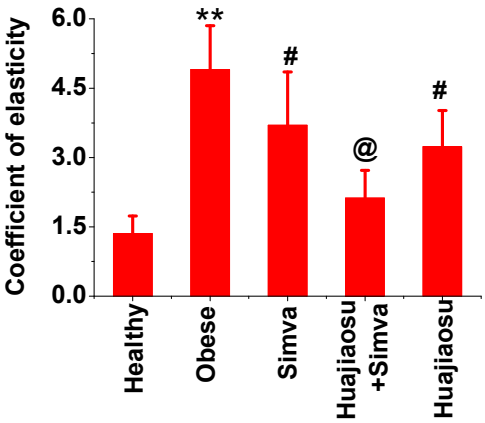

Figure 2. Coefficient of aorta elasticity. The coefficient of elasticity in the obese rats increased, indicating that the vascular elasticity was decreased. Simvastatin or huajiaosu administration alone slightly improved vascular elasticity, while their combination significantly improved vascular elasticity. Simva: simvastatin. ** $P < 0.01$ vs. healthy group; # $P < 0.05$ vs. obese group; @ $P < 0.05$ vs. simvastatin group.

3.4 Effects of huajiaosu on vascular contractile and relaxation functions in obese rats

The vascular contractile and relaxation responses to vasoactive agents are major functions of vascular smooth muscle cells and endothelial cells. Damage to the vascular contractile and relaxation responses affects tissue perfusion and compliance to blood pressure. In the present study, we examined the effects of huajiaosu on the aorta contractile and relaxation responses.

The vascular contractile response of the aorta in obese rats was significantly increased, compared with the healthy rats. Compared with the healthy group, the cumulative dose-response curves of the aorta of obese rats to NE were significantly shifted up, and their E_{max} was significantly increased ($P < 0.05$ or $P < 0.01$). Simvastatin administration slightly decreased the contractile response of the aorta compared with the obese group. Huajiaosu in combination with simvastatin administration abolished the obese-induced increase in the aorta contractile response to NE (Figure 3).

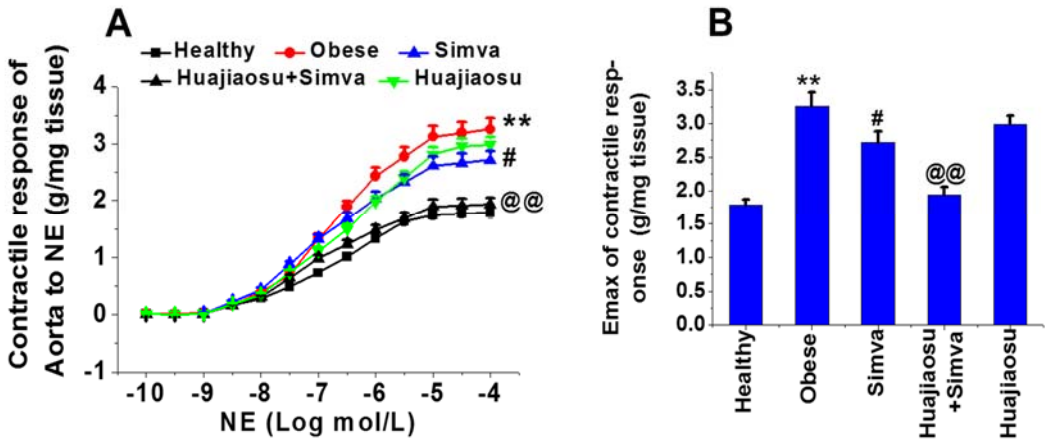

Figure 3. Effect of huajiaosu on the aorta contractile response to NE. A: NE-induced aorta contractile curve. The contractile curve was shifted up in the obese group, whereas simvastatin, huajiaosu or their combination shifted the contractile curve down, with the combination administration showing the most significant effect. B: The E_{max} of the aorta contractile response to NE. The E_{max} of the contractile response was significantly increased in the obese group. Simvastatin in combination with huajiaosu abolished the obese-induced increase. NE: norepinephrine; Simva: simvastatin. ** $P < 0.01$ vs. healthy group; # $P < 0.05$ vs. obese group; @@ $P < 0.01$ vs. simvastatin group.

The aorta relaxation response was significantly decreased in the obese group compared with the healthy rats, and the E_{max} of the relaxation response to acetylcholine decreased from 94.5% in the healthy group to 44.2% in the obese group. Simvastatin administration slightly increased the aorta relaxation response. However, simvastatin in combination with huajiaosu administration significantly reversed the obese-induced decrease in the aorta relaxation response to acetylcholine (Figure 4).

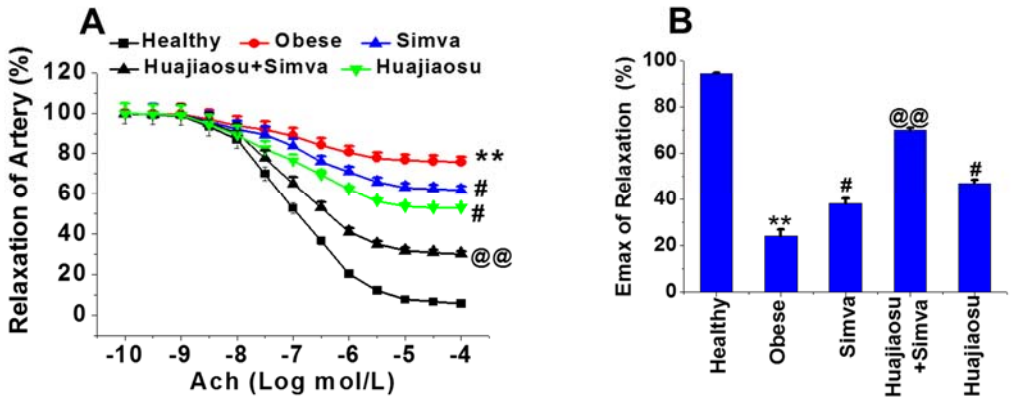

Figure 4. **Effect of huajiaosu on the aorta relaxation response to acetylcholine**. A: relaxation curve of the aorta to Ach. The relaxation curve was shifted up in the obese

group, while simvastatin, huajiaosu or their combination shifted the curve down, with the combination administration showing the best effect. B: E_{max} of the aorta relaxation response to Ach. The E_{max} relaxation response significantly decreased in the obese group, whereas simvastatin in combination with huajiaosu significantly reversed this decrease. Ach: acetylcholine; Simva: simvastatin. ** $P < 0.01$ vs. healthy group; # $P < 0.05$ vs. obese group; @@ $P < 0.01$ vs. simvastatin group.

3.5 Effects of huajiaosu on aorta pathological changes in obese rats

Lipid deposition and vascular calcification are major factors that induce vascular sclerosis. Haematoxylin and eosin staining showed lipid droplet deposition in the aorta of obese rats. Simvastatin administration did not reduce this lipid droplet deposition. However, simvastatin in combination with huajiaosu administration significantly decreased the lipid droplet deposition in the aorta. Silver staining showed that calcium deposition was increased in the aorta of obese rats. Simvastatin administration did not reduce the calcium deposition, while simvastatin in combination with huajiaosu significantly diminished the calcium deposition in the aorta. (Figure5)

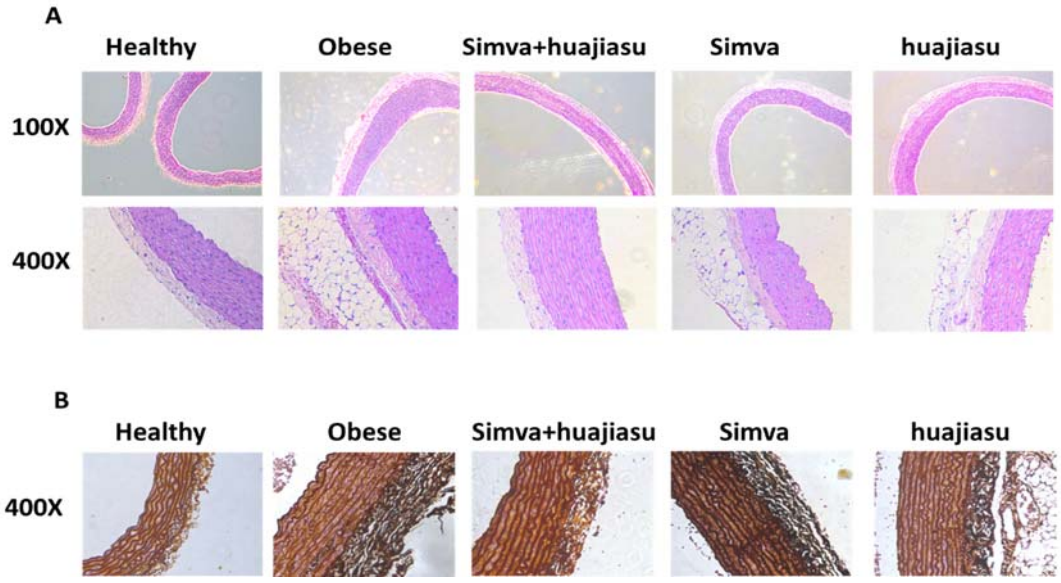

Figure 5. **Effect of huajiaosu on the aorta pathological changes**. A: Haematoxylin and eosin staining; B: Silver staining. The lipid droplet and calcium depositions were increased in the obese group, simvastatin, huajiaosu only slighy decrease the lipid droplet and calcium deposition, combination administration significantly reduced lipid droplet and calcium deposition.

3.6 Effects of huajiaosu on the expression of BMP2 and elastin in the aorta of obese rats

The mechanisms of metabolic diseases inducing vascular complications include lipid deposition and inflammation. A recent study has shown that calcium deposition was an important factor for inducing vascular sclerosis, and that BMP2 was a major molecule controlling vascular sclerosis (14). Our results showed that BMP2 expression was increased in the obese group compared with the healthy group, whereas simvastatin administration slightly decreased this expression. However, huajiaosu in combination with simvastatin administration significantly decreased the BMP2 expression. The expression of elastin was significantly decreased in the obese group, whereas simvastatin or simvastatin in combination with huajiaosu administration increased this expression. The effect of simvastatin in combination with huajiaosu was stronger than that of each agent alone (Figure 6).

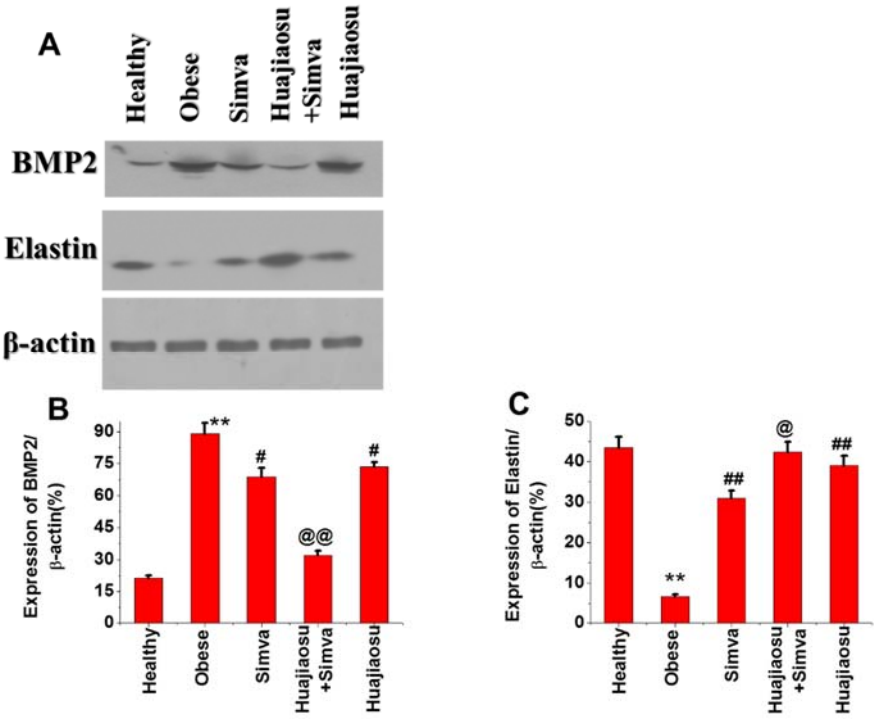

Figure 6. Effect of huajiaosu in combination with simvastatin on the expression of BMP2 and elastin. In obese rats, the expression of BMP2 was increased and the expression of elastin was decreased, compared with the healthy group. Simvastatin or huajiaosu alone only slightly relieved the obesity-induced effect on BMP2 and elastin expression. Huajiaosu in combination with simvastatin abolished the obese-induced effect on BMP2 and elastin expression. A: Western blotting of BMP2 and elastin

expression. B: Quantification of BMP2 expression. C: Quantification of elastin expression. BMP2: bone morphogenetic protein 2. Simva: simvastatin; ** $P < 0.01$ vs. healthy group; # $P < 0.05$, ## $P < 0.01$ vs. obese group; @ $P < 0.05$, @@ $P < 0.01$ vs. simvastatin group.

4. Discussion

Vascular complications are important in high lipid or glucose-induced organ damage in obesity or hyperlipidemia, hence lowering blood glucose and/or lipids are major treatments. Previous clinical and basic studies have demonstrated that lowering blood glucose or lipid levels did not alleviate vascular complications. Simvastatin is a common drug for lowering blood lipid levels. Whether huajiaosu in combination with simvastatin can alleviate vascular complications in obese subjects is unclear.

The present study showed that blood lipids were significantly increased in obese rats. Vascular functions were damaged in obese rats, as we showed that vascular elasticity was decreased, the vascular contractile response was increased and the vascular relaxation response was decreased. Furthermore, the aorta showed lipid and calcium deposition. Simvastatin alone improved the blood lipid level, however, its effect on vascular function improvement was not obvious. Huajiaosu in combination with simvastatin significantly improved vascular functions compared with simvastatin alone; vascular elasticity was increased, the vascular contractile response was decreased and the vascular relaxation response was increased, while the aorta lipid deposition and calcium deposition were alleviated. When we investigated the mechanism, we found that the effects of huajiaosu in combination with simvastatin on vascular functions were associated with the expression of the vascular elasticity proteins, BMP2 and elastin. The expression of BMP2 in obese rats was increased and the expression of elastin was decreased, however, huajiaosu in combination with simvastatin significantly abolished the increase in BMP2 and the decrease in elastin expression.

Huajiao is a common food seasoning, especially in Sichuan, China. Food treatment of metabolic diseases such as diabetes and hyperlipidemia is considered safe (15). Previous studies have shown that many foods have protective effects on organ functions. For example, chili (lajiao) has been demonstrated to have a protective effect on vascular functions in hypertension via transient receptor potential cation channels (16). Red wine protects against vascular sclerosis in elderly people via anti-oxidation. A previous study has found that huajiaosu decreased the blood lipid level in hyperlipidemia (17). Our present study showed that huajiaosu alone at 3 mg/d/kg for 8 weeks did not significantly decrease the blood lipid level, whereas huajiaosu in combination with simvastatin significantly alleviated vascular dysfunction including vascular elasticity, vascular contractile and relaxation responses, and lipid and calcium deposition.

Study limitations. 1. Only 3 mg/d/kg of huajiaosu were used to investigate the effect on vascular functions; whether a lower dosage of huajiaosu has similar effects needs further investigation. 2. We only used rats in the present study and we only examined vascular functions; if these results are to be extrapolated to other animals and organs, further research is required.

5. Conclusions

Obesity induced vascular dysfunction, especially, the vascular elastin decreased. Simvastatin administration decreased the blood lipid level, but it did not improve vascular functions. Huajiaosu in combination with simvastatin improved vascular functions including the vascular contractile and relaxation responses, and vascular elasticity. The beneficial effects of huajiaosu + simvastatin on vascular functions were associated with the expression of BMP2 and elastin.

6. Declaration

The present study was done at the Research Institute of Surgery, Daping Hospital, Third Military Medical University (Chongqing, China) from 2016.3~2017.5.

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致 谢

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同时，在课题执行过程中一些实验方法也得到了多位老师的指导，动物模型制作是在野战外科研究所吴跃老师的指导下完成的，病理切片的制作得到了大坪医院病理科杜娟老师的帮助，朱娱老师教会了我血管环的制作以及血管功能的测定，向鑫明教会了我蛋白组方法学，在此一并感谢。

附：

指导老师 1：陈盛斌，男，38 岁，重庆市南开中学学生处，数学和计算机双学士学位。在教学同时长期同时学生科学研究指导工作，先后指导 20 余学生获得国家级奖励。

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