

# Yiqi Huaju formula, a Chinese herbal medicine, reduces arterial pressure in salt-sensitive hypertension by inhibiting renin-angiotensin system activation

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**Abstract.** Hypertension is a chronic disease with a high prevalence, and is associated with a high risk of vascular disease and premature death. Traditional Chinese medicine has been administered to treat hypertension for many years. In the present study, the effects of Yiqi Huaju formula (YQ; a compound used in traditional Chinese herbal medicine) were observed in salt-sensitive hypertension, which was induced by a high-salt and high-fat (HSF) diet and the potential mechanism was investigated. YQ was prepared from five plant extracts and was dissolved in normal sodium chloride prior to use. Male Sprague-Dawley rats were randomly divided into three groups, and fed either a normal diet (control), an HSF diet or an HSF diet with YQ. At week eight, blood pressure was measured and 24-h urine samples were collected from all of the rats. The rats were subsequently sacrificed, and their blood was collected for biochemical analyses and kidney tissue samples were dissected for the immunohistochemical assay. YQ was observed to decrease the high arterial pressure and serum total cholesterol level, which had been induced by the HSF diet. It also enhanced the excretion of urinary angiotensinogen, Na<sup>+</sup>, and decreased the loss of urinary aldosterone,

K<sup>+</sup> and microalbuminuria. In addition, YQ inhibited the high mRNA expression level of renal renin, angiotensin II (Ang II), and Ang II receptor, type 1 (AT1R), and inhibited the protein expression of renal AT1R and Ang II receptor type 2, which had been induced by the HSF diet. These results indicate that YQ may reduce the arterial pressure in salt-sensitive hypertension via the inhibition of renin-angiotensin system activation.

## Introduction

Hypertension or high blood pressure is a chronic and complex disease. Hypertension increases the risk of cardiovascular diseases, cerebrovascular diseases and premature mortality. According to The World Health Report 2002, ~62% of cases of cerebrovascular disease and 49% of cases of ischemic heart disease are associated with suboptimal blood pressure (systolic >115 mmHg), and hypertension is estimated to cause 7.1 million mortalities annually worldwide (1). Thus, the prevention, treatment and management of hypertension are considered to be major public health challenges.

Hundreds of different high blood pressure therapeutic agents may be administered to treat hypertension, including calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) receptor blockers. However, blood pressure regulation involves the interaction of multiple factors, including the kidneys, the central and peripheral nervous systems, and the endothelial system (2). Single therapeutic agent administration could not achieve adequate blood pressure control. Combination therapy is required in numerous cases for the management of hypertension. However, due to the inadequate effectiveness of current Western antihypertensive therapeutic agents, as well as safety concerns, there is a significant requirement for the development of efficacious pharmaceutical treatment strategies to combat hypertension (3).

Traditional Chinese medicine (TCM), including herbal medicine and acupuncture, has a long history in the treatment of hypertension, due to purportedly lower side-effects compared with modern medicines (4). TCM may be effective

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at a system level and targets a variety of mechanisms compared with Western treatment modalities, which tend to act on one specific target (2). Certain studies have demonstrated that considerable progress has been made in lowering blood pressure using TCM (5-7). Various complementary and alternative medicine (CAM) clinical studies, including a substantial number of randomized controlled trials and systematic reviews, have shown that CAM is effective and safe for the treatment of hypertension (8-11). Furthermore, our previous study showed that Liu Wei Di Huang formula, a Chinese traditional compound, moderately reduces arterial pressure in salt-sensitive hypertension in male rats (2).

Yiqi Huaju formula (YQ) is a traditional Chinese compound recipe containing five medicinal herb extracts; *Astragalus mongholicus*, *Rhizoma Coptidis*, *Pollen Typhae*, *Rhizoma Alismatis* and *Artemisia capillaris*. Our previous population study showed that this formula in combination with antihypertensive drugs exhibited better results in reducing blood pressure compared with antihypertensive drugs alone (12). However, the underlying mechanism has not been completely elucidated. The aim of the present study was to investigate the effect and mechanism of YQ formula on hypertension, which was induced by a high-salt and high-fat (HSF) diet in rats. The findings may provide a novel strategy for the treatment of salt-sensitive hypertension.

## Materials and methods

**Preparation of the YQ formula.** YQ, consisting of five medicinal herb extracts, was provided by the National Engineering and Research Center of TCM (Beijing, China). The mixture of 12 g Huangqi (*Astragalus mongholicus*; 34.4%), 3 g Huanglian (*Rhizoma Coptidis*; 8.6%), 7.5 g Puhuang (*Pollen Typhae*; 21.4%), 5 g Zexie (*Rhizoma Alismatis*; 14.3%) and 7.5 g Yincheng (*Artemisia capillaris*; 21.4%) was macerated for 1 h with 4 liters of distilled water. The filtrate was collected and the residue was decocted again for 1 h with 2 liters of distilled water. The combined filtrates were condensed and ethanol was added (v/v, 3:7), and the supernatants were collected and condensed. The extract was harvested using a vacuum drying method and dissolved in distilled water prior to use in the experiments.

**Experimental design.** Eighteen 8-week-old specific pathogen-free male Sprague-Dawley rats (weight, 180-210 g), purchased from the Super-B&K Laboratory Animal Co., Ltd. (Shanghai, China), were fed and maintained in the animal facilities (Yueyang Hospital) at a temperature of  $23\pm 2^{\circ}\text{C}$  with a relative humidity of 50-80% under a 12-h light/dark cycle. All rats had free access to rat chow (Shenya, Shanghai, China) and water. After 1 week of acclimatization to the laboratory conditions, the rats were allocated randomly to two groups; one receiving a normal diet ( $n=6$ ) and one receiving an HSF diet ( $n=12$ ; 4% NaCl, 18% lard, 8% yolk powder, 2% cholesterol, 0.2% sodium chlorate and 67.8% rat chow) for two weeks. The rats that were fed an HSF diet were then randomly divided into two groups: HSF-fed (without YQ intervention;  $n=6$ ) and YQ (treated with the YQ formula). Rats in the YQ group were given YQ formula by oral gavage (10.65 g/kg/day) every day for six weeks. The body weight of each rat was monitored weekly. All aspects of the present study were approved by the

Animal Care Committee of Shanghai University of Traditional Chinese Medicine (Shanghai, China).

**Blood pressure.** Blood pressure was measured as described in a previous study (2). Briefly, the blood pressure of the rats was measured by the tail-cuff method using a Softron BP-98A Electro-Sphygmomanometer (Softron Bio Tech Co. Ltd., Beijing, China). The blood pressure values were determined as the mean of three separate measurements.

**Sample collection.** At the eighth week, following a 24-h urine collection using metabolic cages, all of the rats were anesthetized with 10% chloral hydrate (0.3 ml/100 g; Sinopharm Chemical Reagent Co., Ltd, Shanghai, China) and blood was collected from the carotid arteries. Blood samples were collected with EDTA 2K tubes (Eppendorf, 5804, Hamburg, Germany) and centrifuged at  $2,500 \times g$  for 10 min for plasma isolation. Part of the blood was collected in plain tubes without anticoagulant, and was clotted and centrifuged ( $2,500 \times g$  for 10 min) for serum isolation. Any plasma, serum and urine samples that were not used immediately were stored at  $-20^{\circ}\text{C}$  or  $-80^{\circ}\text{C}$  until assaying. Kidney tissues were collected for the immunohistological assay.

**Biochemical analysis.** Urinary  $\text{Na}^{+}$  and  $\text{K}^{+}$  concentrations were determined using a flame atomic absorption spectrophotometer (WFX-210; PerkinElmer, Inc. Waltham, MA, USA). Urine creatinine and serum creatinine and microalbuminuria (MAU) were measured using a commercial ELISA kit (Shanghai Hufeng Bio Co. Ltd., Shanghai, China). The plasma renin, Ang II, ACE activity, urinary angiotensinogen (AGT) and aldosterone (ALD) were analyzed by radioimmunoassay. The serum was analyzed for triglycerides, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol with enzymatic assay kits (Shanghai Kexin Biotechnology Biotech Co., Ltd., Shanghai, China).

**Immunohistochemical assay of kidney tissue.** The right kidney was dissected, maintained on ice, sliced in half and fixed in 4% paraformaldehyde at  $4^{\circ}\text{C}$  for 72 h. The sections were dehydrated through an ascending series of ethanol solution, embedded in paraffin and apportioned for the immunohistochemical assay.

The sections were dewaxed with dimethylbenzene and rehydrated with series of ethanol solution (100-40%), then heated under pressure in a retrieval solution (10mM sodium citrate buffer) for 30 min. After blocking with bovine serum albumin (5%, Amresco, Solon, OH, USA), the sections were incubated with rabbit anti-human monoclonal antibodies against angiotensin II type 1 (ab124734) and angiotensin II type 2 (ab92445) (1:2,000, Abcam, Cambridge, MA, USA) for 2 h at room temperature. Then, the sections were incubated in horseradish peroxidase-conjugated secondary antibody (ab6721; 1:1,000, Abcam) at  $37^{\circ}\text{C}$  for 1 h. Finally, the sections were developed using a 3,3'-diaminobenzidine kit (Beyotime Institute of Biotechnology, Nantong, China). Six randomly selected fields from each section were analyzed under a (Nikon 80i, Tokyo, Japan) microscope. The immunohistochemistry index was defined as average integral optical density (AIOD), which was calculated as follows:  $\text{AIOD} = \text{positive area} \times \text{OD} / \text{total area}$ .

Table I. Primer sequence.

Gene	Forward	Reverse
Renin	CGGCATAACAATCGCATC	AAGGGACAAGCACTCATC
Angiotensin II	AATGGAGACGGTCAACAG	AAGGTCAGCGTGTAGATG
Angiotensin II receptor, type 1	CCAGGTCAAGTGGATTTC	TGATGCTGTAGAGGGTAG
GAPDH	CCGAGGGCCCACTAAAGG	GCTGTTGAGTCACAGGAGCAA

*Renal mRNA expression of renin, Ang II and Ang II receptor, type 1 (AT1R).* Total RNA was extracted from 150-200 mg of kidney tissue using an RNeasy Midi kit (Qiagen, Inc., Valencia, CA, USA). The RNA yield and purity were determined by monitoring absorbance at 260 and 280 nm. cDNA was synthesized from total RNA; the sequence of sense and antisense primers (Scientific Multiskan FC, Thermo Fisher Scientific, Inc., Waltham, MA, USA) are presented in Table I. The reverse-transcription quantitative polymerase chain reaction (RT-qPCR) was conducted using an SYBR Green supermix (Takara Biotechnology Co., Ltd., Dalian, China) and performed in an ABI 7500 Real-Time PCR system (Applied Biosystems Life Technologies, Foster City, CA, USA). The relative expression of the target gene mRNA was determined by measuring the cycle threshold (CT) and this was normalized against GAPDH mRNA expression. The fold change was determined using the  $2^{-\Delta\Delta CT}$  method.

*Statistical analysis.* Statistical analysis was performed using SPSS 18.0 (SPSS, Inc., Chicago, IL, USA). Data are presented as means  $\pm$  standard deviation. One-way analysis of variance, followed by the Least Significant Difference or Dunnett's test, was used to analyze the data.  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

*The HSF diet increased rat body weight.* The body weights of the rats all increased with time (Fig. 1). The weights of the 12 rats administered with an HSF diet were markedly higher from the sixth week when compared with the control rats (Fig. 1;  $P < 0.05$ ). No significant difference in body weight was identified between the HSF and YQ groups.

*The HSF diet increased mean arterial pressure (MAP).* The rats that were fed the HSF diet demonstrated significantly higher values for mean arterial pressure (MAP) from the first week compared with the control group (Fig. 2;  $P < 0.05$ ). The two HSF groups maintained a high MAP; however, at the sixth week, the MAP of rats significantly decreased in the YQ group compared with that in the HSF group ( $P < 0.05$ ).

*Biochemical variables are altered by YQ administration.* No significant differences were identified in the plasma renin, Ang II and ACE activity between groups (Fig. 3). However, urinary AGT markedly decreased in the HSF group compared with the control group (Fig. 4;  $P < 0.05$ ). However, urinary ALD,  $\text{Na}^+$  and  $\text{K}^+$  excretion in the HSF group increased significantly compared with the control group (Fig. 4;  $P < 0.05$ ).

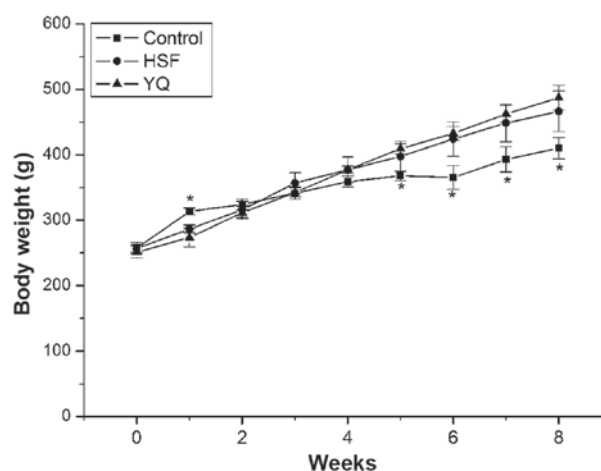


Figure 1. Body weight of the control, the HSF and the YQ-treated rats ( $n=6$ ). The data are presented as the mean  $\pm$  standard deviation. \* $P < 0.05$  vs. the other groups. HSF, high-salt and high-fat diet; YQ, Yiqi Huaju.

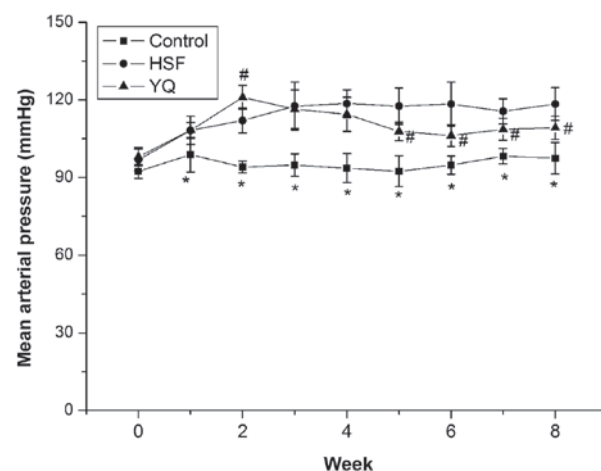


Figure 2. Mean arterial pressure of the control, the HSF and the YQ-treated rats ( $n=6$ ). The data are presented as the mean  $\pm$  standard deviation. \* $P < 0.05$  vs. the other groups; # $P < 0.05$  vs. the HSF group. HSF, high-salt and high-fat diet; YQ, Yiqi Huaju.

No difference in the ratio of urinary  $\text{K}^+$  to  $\text{Na}^+$  was noted between the HSF and control groups. Compared with the HSF group, YQ promoted the excretion of urinary AGT,  $\text{Na}^+$ , and decreased the loss of urinary ALD and  $\text{K}^+$  (Fig. 4). MAU excretion (a sensitive marker of early kidney damage) in the HSF group remained higher when compared with the control group (Fig. 4). Compared with the HSF group, YQ decreased MAU excretion significantly following 6 weeks of treatment ( $P < 0.05$ ).

Table II. Levels of TG, TC, HDL-c and LDL-c.

Plasma lipids	Control (mmol/l)	HSF (mmol/l)	YQ (mmol/l)
TC	2.14±0.16	2.98±0.33 <sup>a</sup>	2.39±0.29 <sup>b</sup>
TG	0.52±0.17	0.54±0.30	0.64±0.37
HDL-c	0.50±0.1	0.25±0.13 <sup>a</sup>	0.49±0.13 <sup>b</sup>
LDL-c	1.60±0.51	1.39±0.52	1.52±0.19

Values are presented as the mean ± standard deviation; <sup>a</sup>P<0.05 vs. the control (normal diet); <sup>b</sup>P<0.05 vs. HSF. TG, triglycerides; TC, cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; HSF, high-salt and high-fat diet; YQ, Yiqi Huaju.

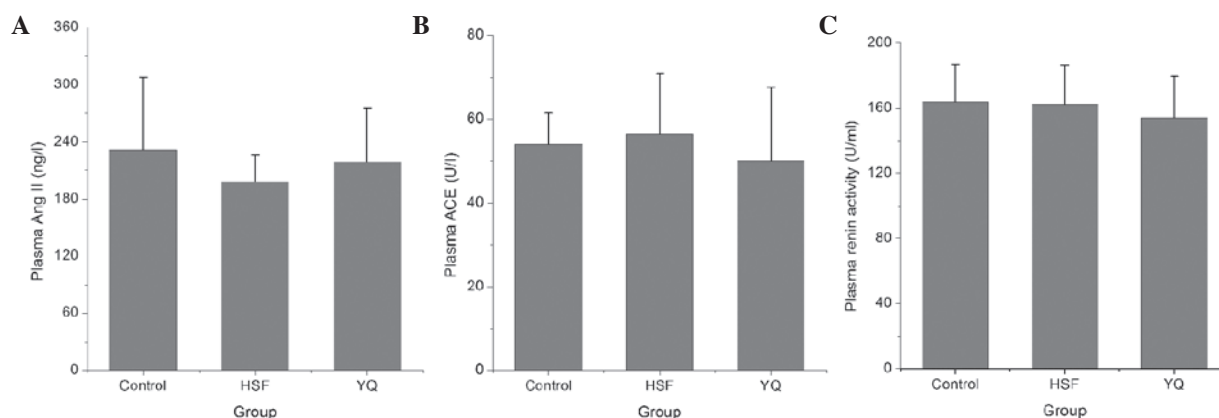


Figure 3. (A) Plasma Ang II, (B) ACE activity and (C) renin levels in the control, the HSF and the YQ-treated rats (n=6). No significant differences were identified in Ang II levels, ACE activity and renin activity between the groups. Ang II, angiotensin II; ACE, angiotensin-converting enzyme activity; HSF, high-salt and high-fat diet; YQ, Yiqi Huaju.

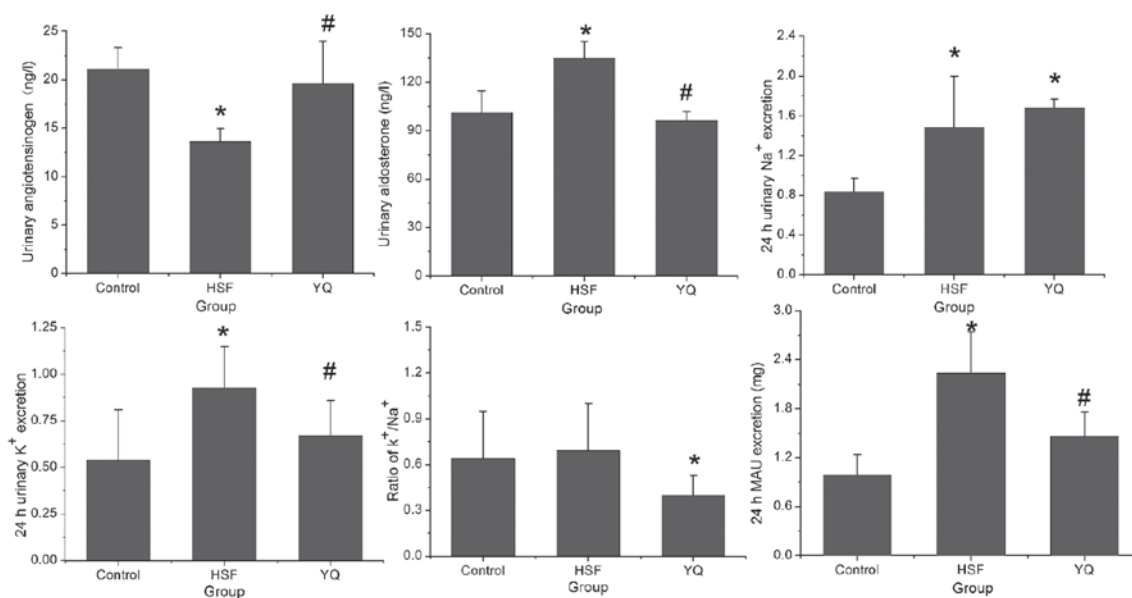


Figure 4. Urinary excretion (angiotensinogen, aldosterone, Na<sup>+</sup>, K<sup>+</sup> and MAU) of the control, the HSF and the YQ-treated rats (n=6). The data are presented as the mean ± standard deviation. \*P<0.05 vs. the other groups; #P<0.05 vs. the HSF group. MAU, microalbuminuria; HSF, high-salt and high-fat diet; YQ, Yiqi Huaju.

Serum lipid levels are presented in Table II. TC is markedly higher in rats in the HSF group when compared with the control and YQ groups (P<0.05). HDL-c appeared significantly lower in the rats in the HSF group compared with the control and YQ groups (P<0.05).

*YQ treatment inhibits renal mRNA expression of renin, Ang II and AT1R.* The renal renin, Ang II and AT1R mRNA expression levels in the HSF group significantly increased compared with the control (Fig. 5; P<0.05). Following six weeks of YQ treatment, renal renin, Ang II and AT1R mRNA expression



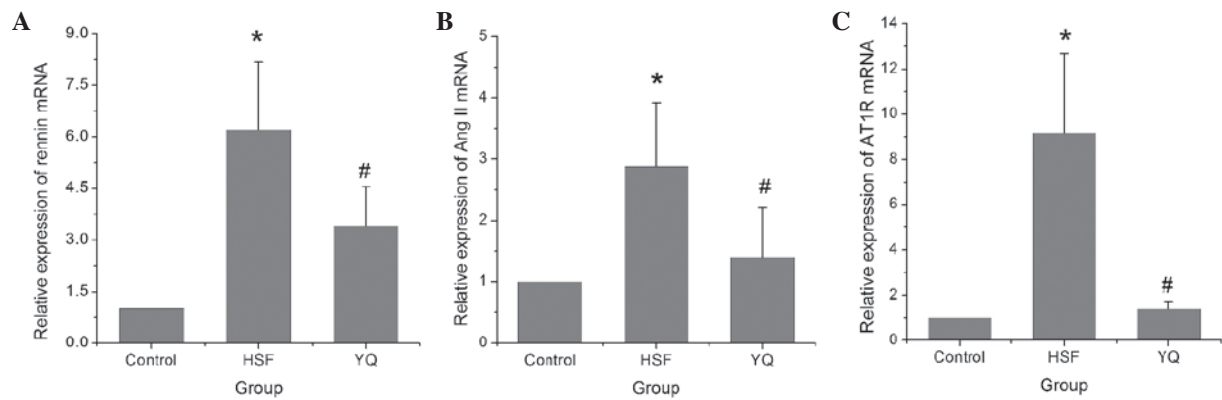


Figure 5. mRNA expression of (A) renin, (B) Ang II and (C) AT1R in the control, the HSF and the YQ-treated rats (n=6). The data are presented as the mean  $\pm$  standard deviation. \*P<0.05 vs. the other groups; #P<0.05 vs. the HSF group. Ang II, angiotensin II; ACE, angiotensin-converting enzyme activity; HSF, high-salt and high-fat diet; YQ, Yiqi Huaju.

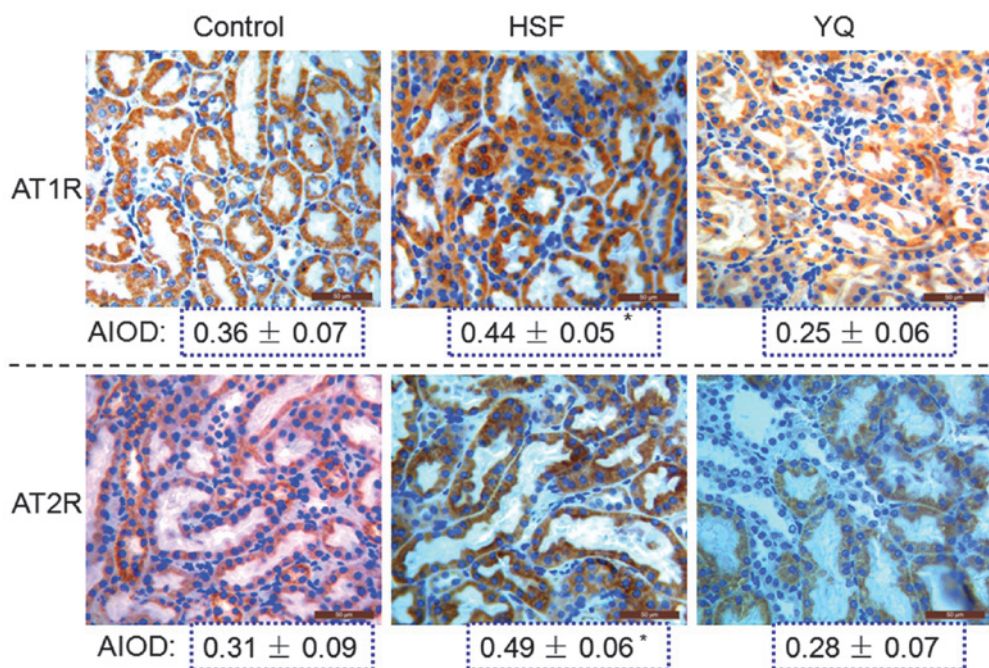


Figure 6. AT1R and AT2R protein expressions in the kidney. AT1R and AT2R expression were increased in the HSF group. YQ significantly inhibited AT1R and AT2R expression. Six randomly selected fields from each section were analyzed under a microscope and hematoxylin was used as a counterstain. The immunohistochemistry index was defined as the AIOD, which was calculated as follows: AIOD = positive area  $\times$  OD/total area. \*P<0.05 vs. the other groups. AT1R, Angiotensin II receptor, type 1; AT2R, angiotensin II receptor, type 2; HSF, high-salt and high-fat diet; YQ, Yiqi Huaju; AIOD, average integral optical density.

levels were significantly inhibited compared with those in the HSF group (Fig. 5; P<0.05).

**AT1R and AT2R protein expression in renal tubules.** AT1R and AT2R protein expression in renal tubules is presented in Fig. 6. AT1R- and AT2R-positive cells were observed in the normal kidney tissues. AT1R and AT2R protein expression in rats that were fed the HSF diet (AIOD: 0.44 $\pm$ 0.05 and 0.49 $\pm$ 0.06, respectively) is markedly increased compared with that in the control group (AIOD: 0.36 $\pm$ 0.07 and 0.31 $\pm$ 0.09, respectively). After 6 weeks of YQ treatment, AT1R and AT2R expression were significantly inhibited (AIOD: 0.25 $\pm$ 0.06 and 0.28 $\pm$ 0.07, respectively) compared with those in the HSF group (P<0.05).

## Discussion

Chinese herbs may potentially be effective for hypertension therapy. In the present study, the effects on salt-sensitive hypertension of YQ formula, a traditional Chinese compound recipe comprising five medicinal herbs, were observed and the potential mechanism was elucidated. The data demonstrated that YQ formula is effective in the treatment of hypertension in rats. In addition, the data showed that YQ formula administration influenced the renin-angiotensin system (RAS), which may be an underlying mechanism for controlling blood pressure.

Despite the availability of numerous antihypertensive agents, blood pressure control and attempts to improve patient

quality of life remain unsatisfactory (13). Hypertension involves multiple systems, including the sympathetic nervous system, the RAS, insulin resistance and renal injury (14-16). The ideal antihypertensive therapeutic agent could control the blood pressure at different levels. TCM may be a potential option for lowering blood pressure, as TCM is capable of functioning at a system level and with various targets. Numerous review articles demonstrated that TCM administered alone or in combination with antihypertensive therapeutic agents may exert certain beneficial effects on patients with essential hypertension (3,6,8). In the present study, the YQ formula was observed to reduce MAP, which was consistent with the findings of our previous population study (12). Furthermore, previous studies identified that Huanglian (*Rhizoma Coptidis*) (17) and Zexie (*Rhizoma Alismatis*) (18), which are important compounds of the YQ formula, lower blood pressure. The present study demonstrates that Chinese herbs or formulae may be administered for the treatment of hypertension.

The effect of YQ formula on the kidneys was also investigated, and the results revealed that in the HSF group daily urinary Na<sup>+</sup> and K<sup>+</sup> excretion was markedly increased. Furthermore, in the HSF group, MAU excretion, a sensitive marker of early kidney injury, remained higher compared with the control group. YQ formula was shown to enhance the excretion of urinary Na<sup>+</sup> and decrease the loss of urinary K<sup>+</sup>. In addition, YQ significantly decreased MAU excretion compared with the HSF group. These findings indicate that YQ may improve renal function, which may be a factor for controlling blood pressure.

The RAS is a predominant homeostatic system that controls body fluid volume, electrolyte balance, blood pressure, and neuronal and endocrine functions associated with cardiovascular control (19). The RAS exerts its effects via its primary effector molecule, Ang II, which binds to specific membrane-bound Ang receptors that are located in various tissues (19,20). Recent studies have revealed that Chinese herbs regulate the function of the RAS, the sympathetic vagus nerve and the immune system by inhibiting the levels of inflammatory factors (21,22). The effect of YQ formula treatment, with regard to the involvement of RAS, was also observed in the present study. The results demonstrated a significantly lower urinary Ang II level in the HSF group when compared with the control group, which was consistent with a previous study (2). Ang II exerts its effects via the activation of AT1R and AT2R (23). Urinary Ang II levels markedly increased in the YQ group compared with the HSF group in the present study. Furthermore, the mRNA expression of renin, Ang II and AT1R, and protein expression of AT1R and AT2R in renal tubules were observed. mRNA expression of renin, Ang II and AT1R in the HSF group were increased compared with the control group, while YQ significantly inhibited the upregulated expression of renin, Ang II and AT1R that was induced by the HSF diet. Similar results were observed in the protein expression of AT1R and AT2R in the renal tubules. Wang and Du (24) demonstrated that AT1R mRNA levels in the aorta and in the mesenteric resistance arteries of Wistar rats fed a high-salt diet were increased. Stewen *et al* (25) identified that AT1R density was increased in the renal cortex of spontaneously hypertensive rats following chronic high-salt intake. The findings noted

above suggest that one of the mechanisms, which resulted in the reduced arterial pressure in the YQ group of the present study, was due to the inhibition of Ang II and renin levels in the kidney, as well as inhibition of AT1R and AT2R expression in the renal tubules. However, further studies are required to fully elucidate the mechanisms.

Certain studies have demonstrated that Chinese herbs lower blood pressure by inhibiting the expression of nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells and inflammatory factors (26), including TNF- $\alpha$  and IL-6, by increasing antioxidant activities (27) or by stimulating the expression of endothelial nitric oxide synthase (28). However, the potential mechanisms of the action of Chinese herbs on hypertension require further investigation.

In conclusion, the present study indicates that YQ reduces MAP in salt-sensitive hypertension. The underlying mechanism may be associated with the effects of YQ on renal function and RAS activation.

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