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Alkaloids of *Nitraria sibirica* Pall. decrease hypertension and albuminuria in angiotensin II-salt hypertension

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[ABSTRACT] In traditional Chinese medicine, *Nitraria sibirica* Pall. (Nitrariaceae) is used to treat hypertension. This study determined the effects of the total alkaloids of the leaves of *Nitraria sibirica* (NSTA) on blood pressure and albuminuria in mice treated with angiotensin II and a high-salt diet (ANG/HS). Adult mice were divided into three groups: control; infused with angiotensin II and fed a diet containing 4% NaCl (ANG/HS; and ANG/HS plus injection of NSTA (1 mg·kg^{-1}·d^{-1}, i.p.). After treatment of these regimens, daily water and food intake, kidney weight, blood pressure, urinary albumin excretion, renal concentrations of inflammatory markers, including soluble intercellular adhesion molecule-1 (sICAM-1) and monocyte chemoattractant protein-1 (MCP-1), and the expression of renal fibrosis markers were determined. Compared to the control group, the ANG/HS group had higher blood pressure and urinary albumin excretion. Treatment with NSTA in ANG/HS mice for three weeks significantly reduced blood pressure and urinary albumin excretion. ANG/HS treatment caused elevated levels of sICAM-1 and MCP-1, as well as increased fibrosis markers. Concurrent treatment with ANG/HS and NSTA attenuated the levels and expression of renal inflammatory and fibrosis markers. Treatment with NSTA effectively reduces hypertension-induced albuminuria through the reduction of renal inflammatory and fibrosis markers.

[KEY WORDS] *Nitraria sibirica*; Alkaloids; Blood pressure; High salt diet; Hypertension; Albuminuria

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Introduction

The prevalence of hypertension continues to increase, and it is estimated that one billion people are affected wide. Among these hypertensive patients, 340 million are in economically-developed countries [1]. Moreover, the pertensive population is subject to a high incidence of cardiovascular and renal diseases [1-2]. In China, a clinical study in 2005 estimated that 2.3 million cardiovascular deaths, and 1.3 million premature cardiovascular deaths, were caused by hypertension [3]. An epidemiological study has shown that the prevalence of hypertension is about 36% in the Xinjiang adult population [4]. Moreover, accumulating data have onstrated a link between albuminuria and cardiovascular disease [5-6]. Therefore, it is important to identify effective strategies to prevent and treat hypertension and albuminuria. Plant-based medicine, which is widely used in China to treat a variety of symptoms related to cardiovascular tions, is potentially useful for the prevention and treatment of various diseases including hypertension [7-8].

Nitraria sibirica Pall. has been used to treat hypertension in Xinjiang, China [3]. *N. sibirica* is spread through the Middle East, Central Asia, and northwest China's desert region, and maintains a balance in the desert ecosystem [3]. Although *N. sibirica* has been used in anti-hypertensive therapy, the mechanisms whereby the extract of *N. sibirica* regulates blood pressure are not clear. Interestingly, a recent study of the effects of a hydroalcoholic extract of the fruits of *N. birica* (NSHE) on vascular function found that it causes vasorelaxation through a nitric oxide (NO)-dependent path-

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way in the endothelium [3]. To determine whether an extract of *N. sibirica* has an effect in the kidney, other than those in the cardiovascular system, its effects in mice treated with angiotensin II and a high-salt diet (ANG/HS) were examined. The ANG/HS model is one of widely-studied models of teinuric hypertension [9-10].

The present study was designed to determine if the total alkaloid fraction of *N. sibirica* (NSTA) has any effect on blood pressure and albuminuria in the ANG/HS model. In addition, whether the protective effects of NSTA in the ANG/HS model are associated with the levels of renal flammatory and fibrosis markers were examined. The results provide crucial information for understanding the role of *N. sibirica* in attenuating hypertension and albuminuria, and identify the promising approach to prevent and treat tension-induced complications using NSTA.

Materials and Methods

Preparation of the total alkaloids of Nitraria sibirica *(NSTA)*

In July 2011 the leaves of *Nitraria sibirica* were collected from Guma, Hotan, Xinjiang Ulghur Autonomous Region, China. The finely ground leaves (8 kg) were mixed with aqueous ammonia (8%), and left one day. The leaf mixture was extracted ten times with $CHCl_3$ at room temperature. The $CHCl_3$ extract was concentrated in vacuum, then dissolved in $CHCl_3$ (1 L) and extracted thirty times with aqueous tartaric acid (3%) (500 mL). This acid extract was adjusted to pH 10 with Na_2CO_3 and extracted fifteen times with $CHCl_3$. After concentration under vacuum, an extract of NSTA for use in *in vivo* studies was obtained. The yield of alkaloids, which were verified by Dragendorff and Bertrand reagents, in the leaf extract of *Nitraria sibirica* Pall is about 1.23%. The extract also included fatty acids and steroids [11].

Animal

Eight-week-old male C57BL/6J mice (Jackson Laboratory, Bar Harbor, ME, USA) were divided into three groups. The normal diet (ND) group consisted of 8-week-old mice fed a normal diet for three weeks. In the angiotensin and high-salt (ANG/HS) group, 8-week-old male mice with 2% isoflurane were anesthetized and an ALZET osmotic pump (Durect Corp., Cupertino, CA, USA) was subcutaneously implanted into each mouse. These mice were fed a high-salt diet (4% NaCl; Harlan, Madison, WI, USA), and mice were intraperitoneally injected with vehicle every day for three weeks. The osmotic pumps infused angiotensin II (Phoenix Pharmaceuticals, Burlingame, CA, USA) at a rate of 400 $ng \cdot kg^{-1} \cdot min^{-1}$, which is an established model of hypertension and renal injury [10]. In the ANG/HS plus NSTA group, 8-week-old male mice were implanted with ALZET osmotic pumps containing angiotensin II (400 $ng \cdot kg^{-1} \cdot min^{-1}$), fed a high-salt diet (4% NaCl), and injected with NSTA (1 $mg \cdot kg^{-1} \cdot d^{-1}$, i.p.) every day for 3 weeks. A dose of 1 $mg \cdot kg^{-1} \cdot d^{-1}$ was used for NSTA treatment because nary data indicated that a lower dose (0.5 $mg \cdot kg^{-1} \cdot d^{-1}$, i.p.) of NSTA did not affect blood pressure in ANG/HS mice [(146 ± 10) mmHg in NSTA group *vs* (154 ± 6) mmHg in ANG/HS group, n = 5]. Since the effects of NSTA on blood pressure were not observed after 3 weeks of treatment in mice fed a normal diet [(116 ± 3) mmHg in NSTA group *vs* (115 ± 2) mmHg in normal control group, n = 5], the ND + NSTA group was not included in this study. Food and water intake were recorded every day. Mice to be euthanized were deeply anesthetized with a triple anesthetic combination (1.9 $mg \cdot mL^{-1}$ xylazine, 0.37 $mg \cdot mL^{-1}$ acepromazine, and 37.5 $mg \cdot mL^{-1}$ ketamine), followed by thoracotomy. The kidneys were then collected and weighed. All mouse cols were approved by the Institutional Animal Care and Use Committee, and were in accord with the requirements stated in the National Institute of Health *Guide for the Care and Use of Laboratory Animals*.

Blood pressure and urinary albumin excretion measurements

At the end of the third week of their different treatments, mice were anesthetized with 2% isoflurane, after which an arterial catheter (MAC-11, Sai Infusion Technologies, Libertyville, IL, USA) was placed in each carotid artery. The catheter was tunneled under the skin, exteriorized, secured at the back of the neck, filled with heparinized saline, and sealed. One day after catheter placement, the blood pressure was measured for 4 h in freely moving mice by means of pressure transducers coupled to a computerized data collection system (EMKA Technologies, Falls Church, VA, USA), as described previously [12]. Mice were placed in individual metabolic cages for urine collection. Twenty-four hours urine samples were collected and used to mine urinary albumin excretion using an ELISA kit (Exocell, Philadelphia, PA, USA).

Isolation of kidneys and preparation of renal homogenates

After three weeks of their different treatments, the kidneys were isolated from treated and control mice. Renal samples from each mouse were homogenized in 10 $mmol \cdot L^{-1}$ potassium buffer (pH 7.7) (1 mL) containing 250 m $mol \cdot L^{-1}$ sucrose, 1 $mmol \cdot L^{-1}$ EDTA, 0.1 $mmol \cdot L^{-1}$ phenylmethylsulfonyl fluoride (PMSF), and 7.5 $\mu L \cdot L^{-1}$ protease inhibitor cocktail (Sigma- Aldrich, Milwaukee, WI, USA). The homogenates were centrifuged for 15 mins at 3 000 *g* and for 30 mins at 11 000 *g*, then collected supernatants were stored at –80 °C. The protocol for homogenate preparation was scribed previously [13].

Measurements of sICAM-1 and MCP-1 levels in renal homogenates

Commercial kits of soluble intercellular adhesion cule-1 (sICAM-1) (Quantikine sICAM-1 Immunoassay, R&D System, Minneapolis, MN, USA) and monocyte chemoattractant protein-1 (MCP-1) (RayBioTech, Norcross, GA, USA) were used to determine the concentrations of these two inflammatory markers in renal homogenates isolated from mice given different treatments. The levels of sICAM-1 and MCP-1 in renal homogenates were normalized with protein concentrations, determined by the Bradford method (Bio-Rad

Laboratories, Hercules, CA, USA).

Western blot analysis

Renal homogenate samples (50 μg) were separated from treated and control mice by electrophoresis on NuPAGE 4%−12% Bis-Tris gel (Invitrogen, Carlsbad, CA, USA) at 125 V for 3 h. The detailed procedures for transfer, blocking, and washing the samples were described previously [14]. The membrane was incubated for 10 h with antibodies of collagen I (Santa Cruz Biotechnology, Santa Cruz, CA, USA), fibronectin (Santa Cruz Biotechnology), or *β*-actin (Sigma-Aldrich, Milwaukee, WI, USA). The membranes were washed several times with Tris-buffered saline and incubated with secondary antibodies for these proteins. The immunoblots using enhanced chemiluminescence (ECL) detection kit (GE Healthcare, Little Chalfont, Buckinghamshire, UK). Expression levels of these proteins were quantified using National Institutes of Health ImageJ software (http://rsb.info.nih.gov/ij/).

Data and statistical analysis

All values are expressed as means ± SE. All data were analyzed by GraphPad Instat Software (LaJolla, CA, USA). One-way ANOVA and Tukey-Kramer tests for multiple comparisons or independent Student's *t* test for unpaired groups were used. Statistical significance was set at $P < 0.05$ or 0.01.

Results

Effects of the total alkaloids of leaves of Nitraria sibirica *(NSTA) on daily water intake, daily food intake, and kidney weight in ANG/HS mice*

Whether NSTA treatment affected water intake, food intake, and kidney weight in a proteinuric hypertensive model induced by treatments of ANG/HS was evaluated. As compared to normal mice, ANG/HS-treated mice increased their daily water intake by 45% and their daily food intake by 47% ($P < 0.05$) (Fig. 1). When ANG/HS mice were treated with NSTA (1 $mg \cdot kg^{-1} \cdot d^{-1}$) for three weeks, it significantly suppressed water intake in mice ($P < 0.05$), but did not affect their food intake. Next, it was determined whether NSTA treatment affected the ratio of kidney-to-body weight in mice given different treatments. It was found that neither ANG/HS nor ANG/HS plus NSTA treatment affected this ratio after three weeks of treatment (Fig. 1C).

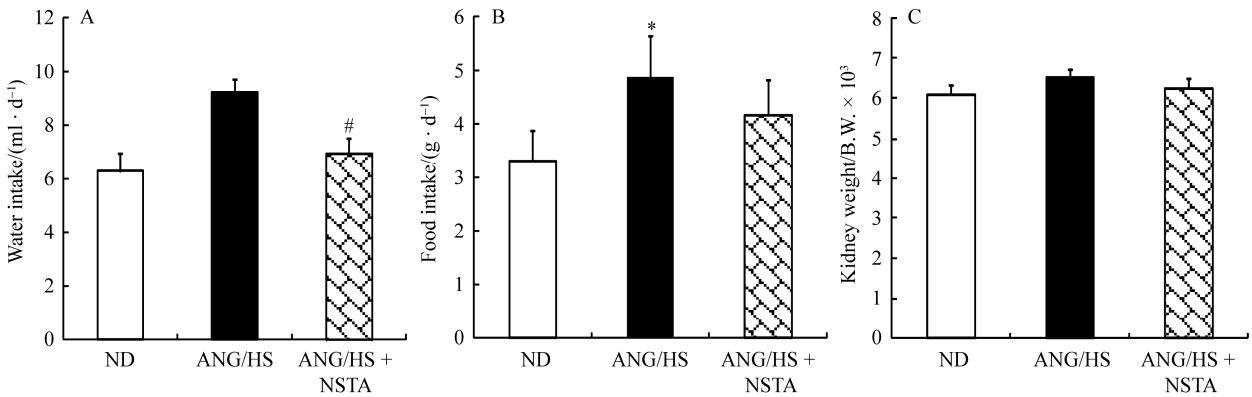

Fig. 1 Effect of ANG/HS-induced hypertension, with or without concurrent treatment with NSTA, on (A) daily water intake, (B) daily food intake, and (C) ratio of kidney-to-body weight during or after three weeks of treatment (means ± SE, $n = 5$). $^{*}P < 0.05$ *vs* ND; $^{\#}P < 0.05$ *vs* ANG/HS

Effects of NSTA on blood pressure and urinary albumin excretion in ANG/HS mice

To determine whether ANG/HS affects blood pressure and urinary albumin excretion in mice, mice were given continuous infusions of angiotensin II, a powerful vasoconstrictor, at a rate of 400 $ng \cdot kg^{-1} \cdot min^{-1}$and fed a high-salt diet for three weeks. After three weeks of ANG/HS treatment, mean arterial pressure (MAP) was significantly elevated, from (118 ± 4) mmHg to (159 ± 5) mmHg ($P < 0.01$; Fig. 2A). In addition, when mice were given ANG/HS for three weeks, the levels of urinary albumin excretion were significantly elevated, from (50 ± 7) to (267 ± 85) $\mu g \cdot d^{-1}$ ($P < 0.01$; Fig. 2B), indicating that ANG/HS caused hypertension-induced albuminuria. Interestingly, chronic administration of NSTA (1 $mg \cdot kg^{-1} \cdot d^{-1}$) significantly suppressed the increase in MAP ($P < 0.01$; Fig. 2A) and urinary albumin excretion ($P < 0.01$; Fig. 2B) induced by ANG/HS treatment.

Effects of NSTA on renal inflammation in ANG/HS mice

Since renal inflammation is an important mechanism for hypertension-induced renal damage, whether NSTA affects the levels of soluble ICAM-1 and MCP-1, two early pro-inflammatory molecules, in the kidneys were evaluated. After three weeks of ANG/HS treatment, levels of MCP-1 ($P < 0.05$; Fig. 3A) and sICAM-1 ($P < 0.05$; Fig. 3B) in renal homogenates were significantly elevated compared with those in normal mice. The increased levels of MCP-1 and sICAM-1 in the kidneys of ANG/HS mice were significantly decreased by treatment with NSTA (Fig. 3).

To further substantiate the effects of NSTA on renal fibrosis, Western blot analysis was used to examine the expression of collagen I and fibronectin in the kidneys of mice

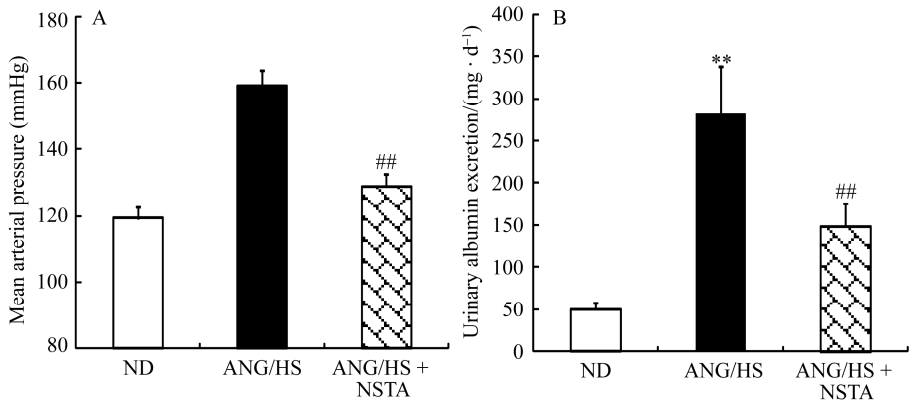

Fig. 2 Effect of ANG/HS-induced hypertension, with or without concurrent treatment with NSTA, on mean arterial pressure (A) and urinary albumin excretion (B) after three weeks of treatment (means ± SE, n = 9). $^{**}P < 0.01$ *vs* ND; $^{\#\#}P < 0.01$ *vs* ANG/HS

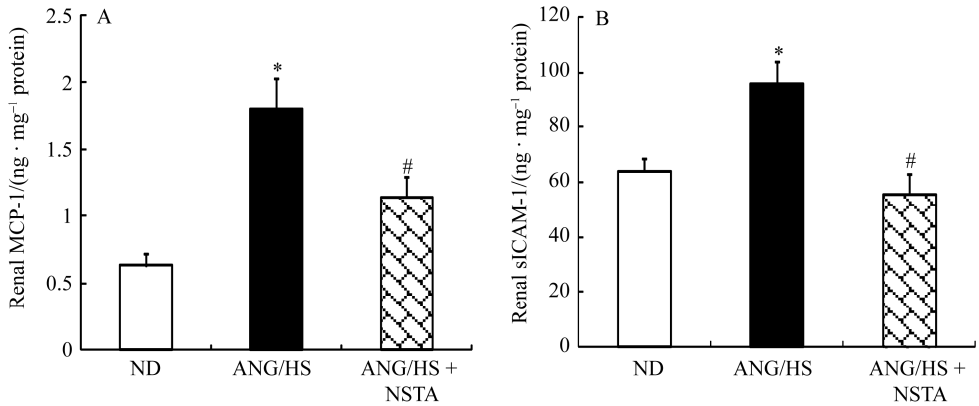

Fig. 3 Effect of ANG/HS-induced hypertension, with or without concurrent treatment with NSTA, on renal levels of (A) MCP-1 and (B) sICAM-1 after three weeks of treatment (means ± SE, n = 5). $^{*}P < 0.05$ *vs* ND; $^{\#}P < 0.05$ *vs* ANG/HS

treated with vehicle, ANG/HS, and ANG/HS + NSTA. ANG/HS significantly induced collagen I and fibronectin expression in the kidneys (Fig. 4A). Densitometry analysis normalized with β-actin showed a 38% increase in collagen I expression and a 73% increase in fibronectin expression in renal samples from ANG/HS-treated mice compared with the vehicle-treated group (Fig. 4B). The induction effects of the expression of collagen I and fibronectin in the kidneys were decreased by concurrent treatment with ANG/HS and NSTA (Fig. 4B).

Discussion

Although *N. sibirica* has been used as a traditional Chinese medicine for anti-hypertensive therapy, its action in hypertension and albuminuria remains unclear. In the present study, the effects of the alkaloids from the leaves of *N. sibirica* (NSTA) in the ANG/HS model were examined in an effort to define the protective action of NSTA, and its association with renal inflammatory and fibrosis markers. It was demonstrated that in the ANG/HS mouse, a well-established model of proteinuric hypertension, the protective effects of NSTA are mediated by reducing blood pressure and urinary albumin excretion.

Although it is interesting that NSTA decreases blood pressure in the ANG/HS model, the mechanism whereby this occurs is still not clear. Interestingly, Senejoux (2012) recently provided important findings regarding the vasorelaxant properties of a hydroalcoholic extract from *N. sibirica* (NSHE). Since the total alkaloids in this study were obtained from the same plant, it is possible that some active alkaloids from the leaves of *N. sibirica* exerted vasorelaxant actions in the blood vessels, therefore contributing to the reduction of blood pressure. Further studies are necessary to isolate compounds from the total alkaloid fraction and identify which specific compounds cause vasodilation in blood vessels.

It is well-established that chronic ANG/HS treatment induces hypertension and albuminuria in mice [10, 15] and rats [16-17]. In addition, the ANG/HS model causes significant renal injury, including hypertrophy [16] and inflammation [15]. In the present study, it was also found that three weeks of ANG/HS treatment caused hypertension and albuminuria (Fig. 2), along with elevation of renal inflammatory and fibrosis markers (Figs. 3 and 4), which are consistent with the characteristics of the ANG/HS model in the literature. However, significant changes in the ratio of kidney-to-body weight (Fig. 1C), an index of renal hyper-

trophy, after ANG/HS treatment, were not observed, indicating that an early stage of renal damage was being examined after the treatment regimens. The reason that the treatment regimens did not cause renal hypertrophy is not clear, but it could be due to the difference of angiotensin II dose and animal species that was used in this study.

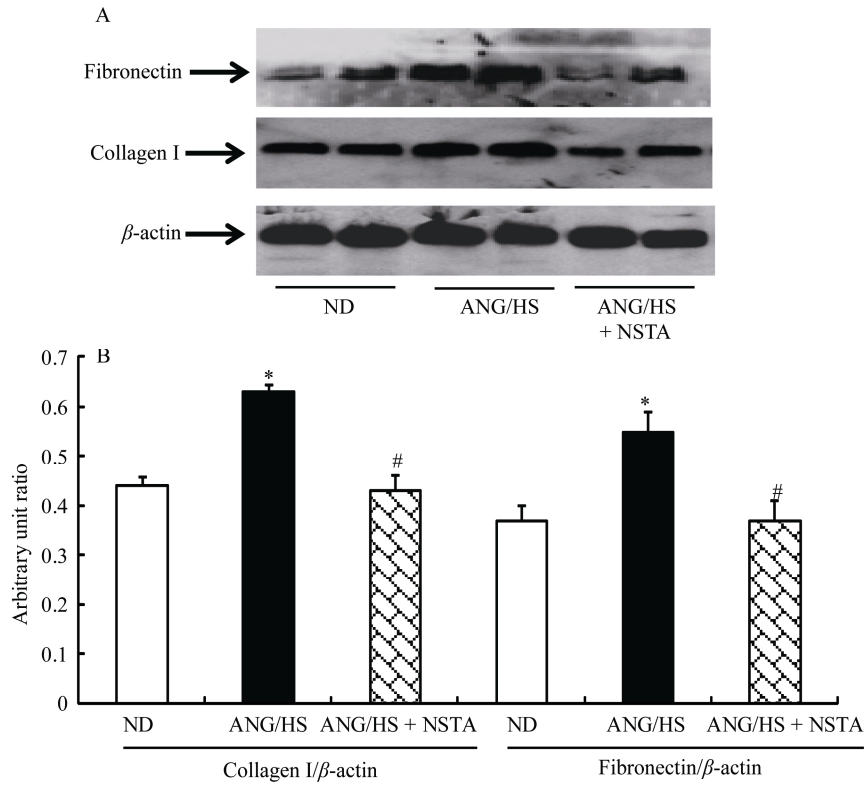

Fig. 4 (A) Representative Western blots of fibronectin, collagen I, and β-actin in the groups of ND, ANG/HS, and ANG/HS + NSTA. (B) Densitometry analysis normalized with β-actin in the groups of ND, ANG/HS, and ANG/HS + NSTA (means ± SE, *n* = 4). **P* < 0.05 *vs* ND; #*P* < 0.05 *vs* ANG/HS

In the present study, an increase in renal levels of MCP-1, an important mediator of inflammation in the kidney was observed [18-19]. MCP-1 is a powerful and specific chemotactic and activating factor for monocyte and macrophage infiltration in the kidneys, which is one of the hallmarks of inflammatory renal damage [20]. Interestingly, previous reports have demonstrated that MCP-1 levels are correlated with renal monocyte or macrophage infiltration in the ANG/HS model [17, 20]. Moreover, elevated levels of soluble ICAM-1, an important inflammatory mediator in the ANG/HS model were observed. This molecule recruits leukocytes by interacting with cognate ligands on leukocytes [17]. The inflammatory responses induced by MCP-1 and ICAM-1 are consistent with the findings that ANG/HS treatment significantly elevated downstream inflammatory markers, including collagen I and fibronectin in the kidneys (Fig. 4). During inflammatory renal injury, this effect is associated with increased production of renal matrix, indicating renal fibrosis. Renal matrix is composed of collagens, including collagen I and other matrix proteins, including fibronectin [21]. The fact that NSTA treatment decreased the expression of collagen I and fibronectin in the kidneys (Fig. 4) demonstrates that treatment with an extract of *N. sibirica* is an effective approach to prevent inflammation-induced renal fibrosis.

Previous phytochemical investigations of *N. sibirica* have led to the identification of bioactive compounds, including alkaloids, that may have diverse biological effects, including compounds that promote antitumor, antidepressant, and anti-inflammatory activities [3, 22]. For example, the alkaloids buphanidrine and distichamine have been shown to have profound effects on the serotonin transporter, which can be used to treat central nervous system disorders [23-24]. In the present study, it was found that an extract of the total alkaloids from *N. sibirica* has protective effects through the reduction of inflammatory and fibrosis markers, which is consistent with the observations that many alkaloids have profound anti-inflammatory activity [22]. Interestingly, a previous report identified several alkaloids, including nitrabirine, deoxyvasicinone, schoberine, and dehydroschoberine in *N. sibirica* [11]. Further studies are needed to identify the specific alkaloids in *N. sibirica* that exhibit anti-inflammatory activity.

The finding that NSTA decreased hypertension and urinary albumin excretion after ANG/HS treatment may have significant clinical implications, because hypertension and microalbuminuria are recognized risk factors for cardiovascular morbidity and mortality [25-26]. Recently, several studies have used traditional Chinese herbs or foods for clinical studies in hypertensive patients [8, 27]. For example, a recent report has demonstrated that an extract of Fufang Danshen (*Salvia miltiorrhiza*), a plant extract that is well tolerated in hypertensive patients, significantly reduces blood pressure and pulse rate [8]. In addition, a research group has determined the effects of Chinese food therapy on hypertensive patients. They demonstrated that after 12 weeks of Chinese food therapy, the intervention group of hypertensive patients required reduced numbers of antihypertensive medications [27]. Since it has been well-established that *N. sibirica* can be used as anti- hypertensive treatment, it will be interesting to see if a randomized, double-blinded, placebo-controlled clinical study using an extract of *N. sibirica* will prevent hypertension and albuminuria in Xinjiang or other areas of China.

In conclusion, this study demonstrates that hypertension induced by ANG/HS is associated with renal damage through the elevation of inflammatory and fibrosis markers. These findings also suggest that chronic administration of an extract of *N. sibirica* reduces blood pressure and inflammation, changes that are associated with the reduction of urinary albumin excretion. This study raises the possibility that, in addition to their blood pressure lowering actions, the alkaloids of *N. sibirica* may act as effective agents against hypertension-induced complications.

Acknowledgments

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