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Mechanism of the diuretic activity of *Descurainia sophia* seed

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Abstract

The diuretic activity of the decoction and the chemical fractions of *Descurainia sophia* was studied with underlying mechanisms in rats. Rat metabolic cage method was used to study the diuretic activity of the decoction and the chemical fractions of *D. sophia*. Western blot, ELISA, ion selective electrode method and cryoscopy method were used to study the underlying mechanism. The urinary output increased significantly in rats administrated decoction. Washing elution fractions had the potent diuretic activity. Washing elution fractions could decrease the urine osmolality, increased the concentration of K^+, and decreased the concentration of Na^+ and ALD, also decreased the expression of aquaporin 1 (AQP1) in kidney. Moreover, compared with washing elution fractions, decoction decreased the levels of AVP, V2R, and AQP2. It is concluded that decoction had significant diuretic activity and washing elution fractions had the potent diuretic activity. The mechanisms of diuretic activity were different between decoction and washing elution fractions.

Introduction

The dry mature seed of *Descurainia sophia* (L.) Webb ex Prantl, which belongs to the Cruciferae family, according to "Shen Nong's Herbal Classic", is bitter in flavor and cool (cold) in nature. It has been used in Traditional Chinese Medicine to purge the lung, relieve asthma, promote water metabolism, and disperse swelling (Zhou et al., 2014). Compounds such as descuraic acid, drabanemoroside, and descurainoside B have been isolated from *D. sophia*. Several studies had reported that *D. sophia* was used for relieving cough, preventing asthma (Nimrouzi and Zarshenas, 2016), promoting urination (Zhou et al., 2014), strengthening heart (Mohamedl and Mahrous, 2009), resisting cancer (Zhou et al., 2014) and adjusting blood fat level.

Edema is abnormal increase or accumulation of fluid in the interstitium (Li and Tang, 2008), which can occur in many parts of human body (Zhou et al., 2014). Diuretics were usually used for edema. However, Traditional Chinese Medicine for edema was also adopted in recent years. *D. sophia* is usually used for asthma due to water retention in the lungs, water distention in the chest and ribs, cough due to the retention of phlegm and fluid, but, the diuretic mechanism of *D. sophia* is not clear. Therefore, these studies on the diuretic activity of the decoction and chemical subdivisions of *D. sophia*, in order to clarify the diuretic mechanism of *D. sophia* and provide a theoretical basis for developing a new diuretic.

Materials and Methods

Plant material

The dried seeds of *D. sophia* were purchased from herbal market in Zhengzhou, Henan province and identified by Prof. Cheng-Ming Dong (Henan Univer-

sity of Chinese Medicine). A voucher specimen (No. 20130715A) was deposited in the Research Department of Natural Medicinal Chemistry, School of Pharmacy, Henan University of Chinese Medicine.

D. sophia (10 kg) was extracted three times with H_2O (100 L × 3) 1 hour each at 100°C. Evaporation of the solvent under reduced pressure provided aqueous extracts (1.14 kg), which were suspended in H_2O (4 L), followed by removal of insoluble materials by centrifugation. The water soluble substances were subjected to Diaion HP-20 macroporous resin column and eluted with ethanol:H_2O (0:100, 20:80, 80:20), successively, to obtain three fractions [Water Part, 20% ethanol elution fraction (20% fraction), 80% ethanol elution fraction (80% fraction)]. Alcohol sink component and washing elution fraction were obtained from Water Part by the technology of alcohol separation. Hydrochlorothiazide was purchased from the Tong Ren Pharmaceutical Co., Ltd. (China) and diluted with water.

Experimental animals

Male Wistar rats (180-220 g) were obtained from Animal Laboratory of Quality Control Center from Shandong Lukang Pharmaceutical Co., Ltd. All the animals were housed under standard environmental conditions (18-22°C) with a 12 hours light-dark cycle, with free access to tap water and standard laboratory rat food. The experiments were conducted in accordance with internationally accepted standard procedures for animal use. Rats were housed individually in a metabolic cage for three days and then followed by two control days. They drink water freely and feeding for 18 hours, then press the abdomen gently at the beginning of the experiment to drain residual urine in the bladder. Before the treatment, all animals received physiological saline at an oral dose of 2.0 mL/100 g to impose a uniform water and salt load, and to collect urine volume in 2 hours. The rats which urine volume was more than 40% saline can be used for experiment.

Diuretic activity of D. sophia decoction on rats

The 40 rats used for experiment were divided into 5 groups according to body weight and urine volume. Five groups are: Control group, hydrochlorothiazide group (17 mg/kg), *D. sophia* group of low dose (117 mg/kg), medium dose (234 mg/kg) and high dose (468 mg/kg). The dosing volume of each rat was 1.0 mL/100 g. Urine volume was collected within 5 hours after orally administration. Orally administrated as above for 4 days continuously and analyzed the change of urine volume in 4 days.

Diuretic activity of different fractions on rats

Seventy-two rats were divided into 7 groups according to body weight and urine volume. Seven groups are: Control group, hydrochlorothiazide group (17 mg/kg), *D. sophia* group, alcohol solution group, washing elution fractions group, 20% fraction group and 80% fraction group. The dosages of other groups were equated to the best dosage of decoction [medium dose (234 mg/kg)]. Their urinary bladders were emptied by gentle compression of the pelvic area. Before the treatment, all animals received physiological saline at an oral dose of 5 mL/100 g to impose a uniform water and salt load (Benjumea et al., 2008). Thirty minutes later, the rats were randomly assigned into 7 groups. Then the rats were placed into metabolic cage. The urine was collected in a graduated cylinder and its volume was recorded at 2 hours intervals for 5 hours. Cumulative urine excretion was calculated in relation to body weight and expressed as mL/100 g. Urine volume was compared of each group.

Diuretic activity of washing elution fraction on rats

Forty-eight rats were divided into 6 groups according to body weight and urine volume. Six groups are: Control group, hydrochlorothiazide group (17 mg/kg), *D. sophia* group, water elution fraction group of low dose, water elution fraction group of medium dose and water elution fraction group of high dose. Administrate as above for 7 days continuously.

Sample collection and biochemical methods

The urine was collected with a metabolic cage, then centrifuged (1000 x g at 4°C), and stored at -80°C until analyzed. Blood sample from the aorta was centrifuged and plasma was collected for Na^+, K^+ and Cl^- measurements with a Beckman AU680 biochemical analyzer. The urine and plasma osmolality were determined by Description OM815 (Loser Messtechnik). The levels of renin (E-EL-R0030c, Elabscience Biotechnology Co. Ltd., China), Ang II (E-EL-R1430c, Elabscience Biotechnology Co. Ltd.), angiotensin converting enzyme (E-EL-R2401c, Elabscience Biotechnology Co. Ltd.), ALD (E-EL-0070c, Elabscience Biotechnology Co. Ltd.), AVP (E-EL-R0045c, Elabscience Biotechnology Co. Ltd.) and AVPV2R (E-EL-R0766c, Elabscience Biotechnology Co. Ltd.) of blood plasma were determined by ELISA method. Absorbance of standards and samples were determined spectrophotometrically at 450 nm using a microplate reader. Results were plotted against the linear portion of a standard curve.

Western-blotting detected kidney AQP1 and AQP2

The animal kidneys were removed in toto, and the serosal surface was dissected carefully. The kidney of each rat was snap frozen in liquid nitrogen and kept at -80°C for molecular studies. The cortex and medulla of the kidney were separated and immediately frozen in liquid nitrogen at -80°C. Proteins from the cortex and medulla were extracted with a mammalian protein extraction kit (Beijing ComWin Biotech Co., Ltd., China). Proteins were quantified using the Bradford

Table I

Effect on rats' total urine volume in 5 hours after administrating decoction (mL/100 g)

Groups	Dose (mg/kg)	1st day	2nd day	3rd day	4th day
Control group	–	2.6 ± 0.2	2.5 ± 0.5	1.9 ± 0.3	2.1 ± 0.3
Hydrochlorothiazide	17.0	5.3 ± 1.2[b]	5.0 ± 0.5[b]	4.7 ± 1.0[b]	4.5 ± 0.4[b]
Low dose	117.0	2.8 ± 0.5	2.1 ± 0.9	2.5 ± 0.4	2.8 ± 0.6[a]
Medium dose	234.0	2.5 ± 0.2	2.6 ± 0.9	2.7 ± 1.0[a]	2.8 ± 0.8[a]
High dose	468.0	2.3 ± 0.2	2.3 ± 0.4	2.9 ± 0.4[a]	2.8 ± 0.5[a]

Values are expressed as mean ± SD of eight rats in each group. [a]p<0.05; [b]p<0.01 compared to control group using Student's t-test

Table II

Effect of each chemical subdivision of *D. sophia* on rats' urine volume (mL/100 g)

Groups	Dose (mg/kg)	1 hour	3 hours	5 hours	Total in 5 hours
Control group	–	1.0 ± 0.3	0.9 ± 0.4	0.6 ± 0.2	2.8 ± 0.6
Hydrochlorothiazide	17.0	2.4 ± 0.4[b]	2.2 ± 0.4[b]	1.3 ± 0.3[b]	6.1 ± 0.5[b]
D. sophia	234.0	1.7 ± 0.5[b]	1.5 ± 0.3[a]	1.0 ± 0.2[a]	4.2 ± 0.6[b]
Alcohol solution	60.9	1.6 ± 0.4	1.6 ± 0.4[a]	0.8 ± 0.2	3.7 ± 0.5[a]
Washing elution fraction	119.5	1.9 ± 0.3[b]	1.6 ± 0.5[b]	1.1 ± 0.5[b]	4.5 ± 1.1[b]
20% fraction	22.9	1.4 ± 0.7[a]	1.6 ± 0.5[a]	1.0 ± 0.5[a]	4.0 ± 1.4[a]
80% fraction	13.9	1.3 ± 0.3	1.5 ± 0.5[a]	0.8 ± 0.2	3.3 ± 0.7

Values are expressed as mean ± SD of eight rats in each group. [a]p<0.05; [b]p<0.01 compared to control group using Student's t-test. All rats were pre-treated with an oral dose of 5 mL/100 g body weight of normal saline prior to the administration of the test substances

protein assay kit (Wuhan Boster Biological Technology, Ltd., China). Samples were separated on 4 and 12% SDS gels and transferred onto nitrocellulose membranes. Membranes were blocked overnight at 4°C with 5% dry milk in TPBS (PBS containing 0.1% Tween 20), and then incubated with the appropriate primary antibodies (AQP1, GR270583-4, 1:500, Abcom, UK; AQP2, GR107654-2, 1:500, Abcom, UK) for 2 hours at room temperature. After washing with TPBS, membranes were incubated with horseradish peroxidase-linked secondary antibodies (1:2000 dilution with TPBS containing 5% dry milk) at room temperature for 1-2 hours. Chromogenic reaction with ECL kit to chromogenic, and collect protein bands with chemiluminescence apparatus (azure c500), and analyze bands with quantity one software. Protein densitometric analysis was performed with normalization against β-actin.

Statistical analysis

The results were expressed as the mean ± SD (Standard Deviation of mean). The statistical differences between the negative control and the test fractions were assessed by analysis of variance (ANOVA) followed by Student's t-test for multiple comparisons. For comparisons with the negative control groups, p values less than 0.05 were considered significant.

Results

Effects of decoction on urinary volume

Daily administration of decoction for 4 days significantly increased diuresis after the 3rd day of treatment (p<0.05). Compared with the control group, medium dose of decoction had the potent diuretic activity. The 117.0, 234.0 and 468.0 mg/kg doses of *D. sophia* increased the urinary output in 5 hours and not showed a dose-dependent diuretic activity (Table I).

Effects of chemical subdivision of D. sophia on urinary volume

Compared with control group, the results showed that each chemical subdivision of *D. sophia* could increase the urinary output except 80% ethanol elution fraction. Washing elution fraction had the potent diuretic activity (62.9%, p<0.01), 20% ethanol elution fraction and alcohol sink components also could increase the urinary output (44.1%, 35.6%, p<0.05). From the results of total urine volume in 5 hours, washing elution fraction (119.5 mg/kg) had better diuretic activity than decoction (*D. sophia* 234.0 mg/kg) (Table II).

Effects of washing elution fractions on urinary volume

Compared with control group, we found that urinary

Table III

Effect of washing elution fraction on rats' urine volume (mL/100 g)

Group	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
Control group	1.8 ± 0.6	2.1 ± 0.5	1.8 ± 0.4	1.5 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	1.8 ± 0.2
Hydrochlorothiazide (17 mg/kg)	3.5 ± 0.8[b]	3.8 ± 1.0[b]	3.6 ±0.7[b]	4.0 ± 1.0[b]	4.2 ± 0.9[b]	3.9 ± 0.6[b]	3.9 ± 1.2[b]
D. sophia (234 mg/kg)	1.9 ± 0.3	2.7 ± 0.5	2.8 ± 0.7[a]	2.7 ± 0.2[b]	2.8 ± 0.2[b]	2.9 ± 0.5[b]	3.1 ± 0.4[b]
Washing elution fraction (60 mg/kg)	1.6 ± 0.2	2.3 ± 0.2	2.3 ± 0.3	2.0 ± 0.6	2.3 ± 0.3[a]	2.6 ± 0.3[a]	2.6 ± 0.2[a]
Washing elution fraction (119.5 mg/kg)	1.6 ± 0.3	2.8 ± 0.6	2.9 ± 0.5[a]	2.3 ± 0.4[a]	3.0 ± 0.6[b]	3.1 ± 0.5[b]	3.0 ± 0.8[b]
Washing elution fraction (238.9 mg/kg)	2.1 ± 0.6	2.1 ± 0.3	2.0 ± 0.3	2.0 ± 0.3	1.9 ± 0.5	2.4 ± 0.7[a]	2.9 ± 0.7[a]

Values are expressed as mean ± SD of eight rats in each group. [a]p<0.05; [b]p<0.01 compared to control group using Student's t-test

volume was increased after treatment with washing elution fraction from day 3 but not in a dose- and time-dependent manner, and the 119.5 mg/kg doses of washing elution fractions increased the urinary output (64.4%, p<0.05). From the results of urine volume in 7 days, urine volume was with an increase tendency at the first day and second day after administrating washing elution fractions (including low, medium, high dose), but at the third day it increased significantly with medium dose of washing elution fractions (p<0.05). Urine volume increased significantly at 4th day after administrating *D. sophia* (p<0.01) and it increased significantly at fifth day after administrating washing elution fractions with medium dose (Table III).

Table IV

Effect of washing elution fraction on rats' urine and plasma osmolality

Groups	Urine osmotic (moms)	Plasma osmotic (moms)
Control group	925.7 ± 37.2	304.1 ± 5.1
Hydrochlorothiazide (17 mg/kg)	470.8 ± 40.0[b]	271.5 ± 7.5[b]
D. sophia (234 mg/kg)	618.8 ± 64.3[b]	291.3 ± 4.8
Washing elution fraction (60 mg/kg)	633.5 ± 84.7[b]	298.4 ± 5.2
Washing elution fraction (119.5 mg/kg)	570.2 ± 134.3[b]	296.6 ± 6.1
Washing elution fraction (238.9 mg/kg)	539.5 ± 43.6[b]	295.8 ± 5.7

Values are expressed as mean ± SD of eight rats in each group. [a]p<0.05; [b]p<0.01 compared to control group using Student's t-test

Effects of washing elution fractions on urinary and plasma osmolality

Urinary osmolality was decreased significantly after treatment with washing elution fractions (38.4%) and *D. sophia* (33.1%) (p<0.01). Plasma osmolality was not change after treatment with washing elution fractions and *D. sophia*. As positive control, hydrochlorothiazide significantly decreased the level of urinary and plasma osmolality (Table IV).

Effects of washing elution fractions on plasma electrolyte level and RAAS system

Compared with the control group, the 119.5 mg/kg dose of washing elution fractions increased the concentration of K^+ (9.5%) and decreased the concentration of Na^+ (1.7%) similar as *D. sophia*. However, hydrochlorothiazide decreased the concentration of Na^+ and Cl^- (2.4%, 5.7%) significantly (p<0.01) (Table V).

The results also showed that the 59.7 and 119.5 mg/kg dose of washing elution fractions decreased the level of ALD similar as *D. sophia* (Table V). The level of renin, Ang II, and ACE were not changed (data are not shown).

Effect on AVP-V2R-AQP2 axis and the expression of AQP1 in kidney cortex

The level of AVP in plasma was reduced after treatment with 59.7 and 119.5 mg/kg dose of washing elution fractions and *D. sophia*. To determine whether washing elution fractions alter the expression of renal V2R and AQP2, we examined the expression of V2R and AQP2 protein in medulla. We found that washing elution fractions had no activity on the expressions of V2R and AQP2, while *D. sophia* and hydrochlorothiazide decreased the levels of V2R and AQP2 in kidney medulla significantly (p<0.05). That is to say, washing elution fractions can't regulate the level of the components of the AVP-V2R-AQP2 axis in rats, whereas treatment with *D. sophia* and hydrochlorothiazide could increase the level of these components of the AVP-V2R-AQP2 axis.

In addition, we also examined the expression of AQP1 in kidney cortex. The results show that the 59.7 and 119.5 mg/kg dose of washing elution fractions and DS decreased the expression of AQP1 in kidney, while

Table V

Effect of washing elution fractions on the serum electrolyte, ALD, AVP and AVPV2R levels

Group	K^+ (mmol/L)	Na^+ (mmol/L)	Cl^- (mmol/L)	ALD (pg/mL)	AVP (pg/mL)	AVPV2R (pg/mL)
Control group	4.3 ± 0.3	140.4 ± 1.30	102.3 ± 1.3	213.1 ± 18.1	6.4 ± 0.7	63.3 ± 4.6
Hydrochlorothiazide (17 mg/kg)	4.4 ± 0.1	136.9 ± 0.13[b]	96.5 ± 1.1[b]	206.0 ± 42.2	5.9 ± 0.4	56.7 ± 5.1[a]
D. sophia (234 mg/kg)	5.0 ± 0.2[a]	138.1 ± 0.88[b]	101.0 ± 1.4	183.7 ± 17.7[a]	5.9 ± 0.4[a]	56.5 ± 3.6[a]
Washing elution fraction (60 mg/kg)	4.4 ± 0.3	138.6 ± 0.71[b]	101.4 ± 2.0	182.4 ± 18.9[a]	5.7 ± 0.3[a]	57.4 ± 2.0
Washing elution fraction (119.5 mg/kg)	4.7 ± 0.2[a]	138.0 ± 0.9[b]	100.8 ± 1.2	184.5 ± 18.1[a]	5.7 ± 0.7[a]	59.1 ± 4.9
Washing elution fraction (238.9 mg/kg)	4.5 ± 0.3	138.4 ± 0.7[b]	101.2 ± 2.2	222.8 ± 10.9	6.5 ± 0.3	67.2 ± 8.2

Values are expressed as mean ± SD of eight rats in each group. [a]p<0.05; [b]p<0.01 compared to control group using Student's t-test

hydrochlorothiazide had no effect on the expression of AQP1 in kidney (Tables V and Figure 1).

Discussion

Rat metabolic cage method has been used to study diuretic activity of *D. sophia* (Junior et al., 2011). The results showed that 234.0 and 468.0 mg/kg dose of decoction had better diuretic activity and the 234.0 mg/kg dose was optimal. To explore the material basis of *D. sophia* which causes the diuretic activity, the dose of chemical subdivision was converted to the 234.0 mg/kg dose of decoction according to their yield. The results showed that washing elution fractions, 20% ethanol elution fractions, and alcohol sink components had diuretic activity and the diuretic activity of washing elution fraction was the potent.

To further explore its mechanism of promoting urination, washing elution fractions were studied in the experiment. The results showed that the 119.5 mg/kg doses of washing elution fractions increased the urinary output and decreased the urine osmolality, increased the concentration of K^+ and Na^+ of serum, but had no influence on the concentration of Cl^-. Hydrochlorothiazide could decrease the concentration of Na^+ and Cl^- of serum significantly. Hydrochlorothiazide is a typical medicine of diuretic, that increases the urinary excretion of sodium by inhibiting the Na^+/Cl^- symporter (co-transporter system) in the distal convoluted tubule. The results showed that diuretic mechanism of *D. sophia* is different from that of hydrochlorothiazide. *D. sophia* restrains Na^+-K^+ change of distal convoluted renal tubule and collecting duct to retain Na^+ and excrete K^+, which has a similar activity as spironolactone (Schrijver and Weinberger, 1979).

Both circulatory and tissue RAAS have been found to be essential for regulation of the functions of the whole body, organs, tissues and cells. There is no doubt that the RAAS plays fundamental physiological roles in maintaining homeostasis. Angiotensinogen generates angiotensin I under the influence of renin and angiotensin II under the influence of ACE, and angiotensin II stimulates the secretion of aldosterone directly (Mar-

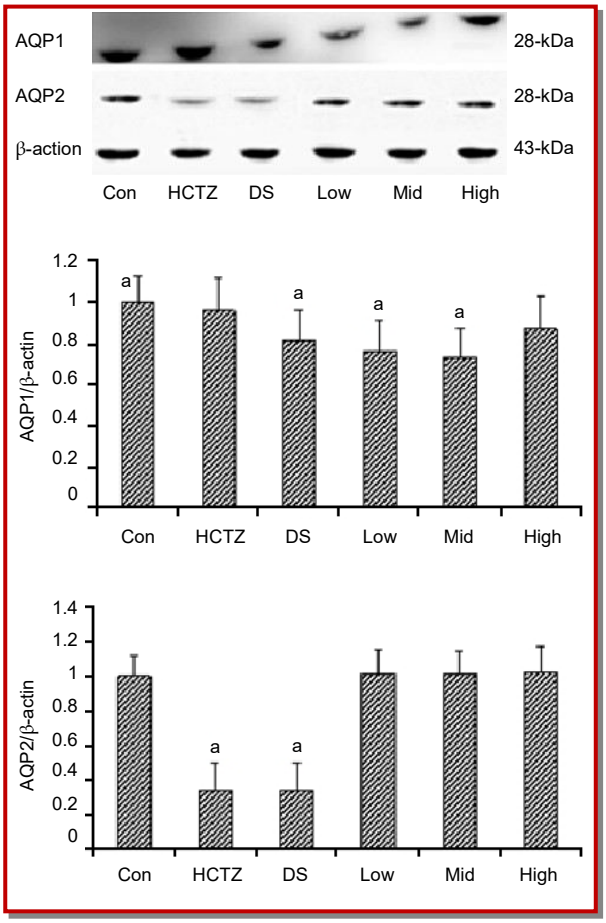

Figure 1: The expression of AQP1 in kidney cortex and AQP2 in kidney medulla tested by Western-blot method

Con is control group, HCTZ is hydrochlorothiazide group, DS is *D. sophia* decoction group, Low is water elution fraction with low dose group, Mid is water elution fraction with middle dose group, High is water elution fraction with high dose group

tinez-Aguayo et al., 2010; Lemmer et al., 2000). Aldosterone can promotes resorption of Na^+ and water in kidney to reduce urine volume (Firsov et al., 2012). The results showed that the 59.7 and 119.5 mg/kg dose of washing elution fractions decreased the level of ALD but had little activity on other items of RAAS system. The reason may be related to that *D. sophia* affect the synthetic of aldosterone (Yuan et al., 2004), its mechanism needs further study.

AVP-V2R-AQP2 axis is also one main links of water metabolism of body, AVP regulates vascular tone through V1 receptors located in the peripheral vasculature, and plasma osmolality via V2R in the kidney, promoting water retention (Judith Radin et al., 2012). AVP binds to the V2R at the basolateral membrane and activates protein kinase A (PKA). By elevating cAMP levels with forskolin, AQP2 is translocated to the apical plasma membrane. AQP2 exerts its effect through a cycle of water endocytosis and exocytosis (Bustamante et al., 2004; Arthur et al., 2015). In our study, the diuretic mechanism of decoction included a decrease in AVP, its receptor V2R and the regulated-protein AQP2. AQP2 is the most important aquaporin, and plays critical role in some diseases. The regulation of AQP2 expression was mainly by AVP signaling. Although our results suggested that decoction significantly decreased the levels of renal AQP2 expression in rats, the changes of AVP levels in plasma and V2R were subordinate. Therefore, both AVP signaling-dependent and-independent ways might contribute to the mechanism underlying the suppression of AQP2 expression by decoction. Interestingly, washing elution fractions had no influence on AVP-V2R-AQP2 axis. The reason may be related to that washing elution fractions is one of fractions of *D. sophia*, each batch of split fractions of *D. sophia* do not cross (Zhang et al., 2015). In our later study, results show that 20% ethanol elution fraction play diuretic activity through regulating AVPV2R-AQP2 axis.

Aquaporins (AQPs) are a family of small, integral membrane proteins that transport water and, in some cases, water and glycerol. Kidney is main organ to adjust water balance of body, which includes highest content of AQPs (Terris et al., 1996). Most reabsorption in the proximal tubule occurs constitutively, with water movement being facilitated by AQP1 and AQP1 plays an important role in the thin descending limb of the loop of Henle. The 59.7 and 119.5 mg/kg doses of washing elution fractions significantly decrease AQP1 level and increase urine volume, which may be related to washing elution fractions decrease the urine osmolality (Ma et al., 1998).

Conclusion

The diuretic activity of decoction is remarkable, and the 234.0 mg/kg dose of decoction has the potent diuretic activity. Washing elution fractions, 20% ethanol elution fractions, and alcohol sink components have diuretic activity and the diuretic activity of washing elution fraction is the most potent. Washing elution fractions can decrease urine osmolality, increase the concentration of K^+, decrease the concentration of Na^+ and restrain the expression of AQP1 in kidney and inhibition RAAS system. The consumption of washing elution fractions is less than half of decoction, but with the similar or better diuretic activity. However, decoction can restrain AVP-V2R-AQP2 axis at some extent but washing elution fractions does not. In later experiment, 20% ethanol elution fraction is found to restrain AVP-V2R-AQP2 system.

Ethical Issue

The study was conducted in accordance with the Experimental Animal Administration regulations issued by the State Committee of Science and Technology of the People's Republic of China. The ethical approval reference number of the study is SYXK2010-004. All the procedures for the care of the rats were in accordance with the institutional guidelines for animal use in research.

Conflict of Interest

The authors declare no conflict of interest.

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