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Original Article

Catalpol attenuates blood pressure and improves renal function in spontaneously hypertensive rats

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Abstract: Objective: To investigate the antihypertensive and renal protective effects of catalpol on spontaneously hypertensive rats. Methods: Healthy, specific-pathogen-free (SPF) rats and SPF spontaneously hypertensive (SHR) rats aged 16 weeks were randomly divided into 5 groups: the healthy control group, the SH model group, the low-dose group (10 mg/kg·d^{-1}), the middle-dose group (50 mg/kg·d^{-1}), and the high-dose group (100 mg/kg·d^{-1}). The rats in each group were injected with the corresponding drugs and saline vehicles intraperitoneally every day. The rats' systolic and diastolic blood pressure were measured before the administration of the drugs, at 4 weeks after the first administration of the drugs, and at 8 weeks after the first administration of the drugs. Urine and serum samples and the right kidneys from the rats were collected at 8 weeks post-administration. The urine RBP, Cys-C, β2-MG, and mALB levels and the serum Scr, BUN, AngII, AVP, and ET-1 levels were assessed. The wet weight of each right kidney was measured and the right kidney mass indexes were calculated. Results: After 4 and 8 weeks of catalpol administration, the blood pressure levels in the SHR rats after the intraperitoneal injection of catalpol was significantly lower than the blood pressure levels in the blank control group ($P<0.05$), and the right kidney mass index in the SHR group was significantly higher than it was in the blank control group ($P<0.05$). The urine RBP, Cys-C, β2-MG, and mALB levels and the serum Scr, BUN, AVP, AngII, and ET-1 levels were significantly lower than they were in the blank control group ($P<0.05$). There was a significant dose dependence between the test results of all the indexes and the dose of catalpol ($P<0.05$). Conclusion: Catalpol presents promising antihypertensive and renal protective effects on SHR rats in a dose dependent manner. It can effectively reduce the serum AVP, AngII, and ET-1 levels, decrease blood pressure, and protect renal function.

Keywords: Catalpol, spontaneously hypertensive rats, blood pressure, renal function

Introduction

Chronic kidney disease is a major global health concern with limited therapeutic options. One of the causes of chronic kidney disease is long-term hypertension, and this renal condition is known as hypertensive nephropathy. Presently, hypertensive nephropathy accounts for the second most-common cause of end-stage renal disease [1], which requires regular dialysis and significantly decreases the patients' quality of life. The pathology of hypertensive nephropathy includes ischemic lesions of the glomerulus and renal tubules, which lead to the shrinkage and collapse of the glomerular capillaries, the thickening and hardening of the capillary walls and cystic walls, the proliferation of the mesangial matrix and renal interstitial collagen fibers, and eventually the development of renal failure [2-4]. Current therapies for early stage hypertensive nephropathy include the rational use of renin-angiotensin-aldosterone (RAAS) blockers, and more importantly the maintenance of blood pressure below a certain limit (<130 mmHg) [1]. Traditional Chinese medicine has generated increasing interest among researchers and clinicians for the management of blood pressure and the promotion of renal function [5, 6]. Catalpol is a kind of iridoid glucoside compound extracted from fresh *Rehmannia glutinosa*, which has anti-inflammatory, anti-cancer, diuretic, neuroprotective, hypoglycemic, and anti-hepatitis virus effects [7]. Some studies have reported that catalpol has renal protective effect on diabetic nephropathy rats and mice [8], but the therapeutic effect of

catalpol on hypertensive nephropathy has not been reported. In this study, SHR rats with long-term hypertension were used as the research objects, and the effects of different catalpol dosages on blood pressure and renal function were investigated. Our study provides theoretical support for the potential application of catalpol for hypertensive nephropathy treatment.

Materials and methods

Experimental materials

A total of 32 male SPF SHR rats aged 16 weeks, and 8 male SPF Wistar-Kyoto (WKY) rats aged 16 weeks were purchased from the Beijing Vital River Laboratory Animal Technology Co., Ltd. with license number SCXK (Beijing) 2016-0611. The rats were reared in a laminar flow purification laboratory of an animal experiment center. A drug sprayer was used daily to prepare a 0.1% povidone iodine solution for air disinfection. Aseptic padding was replaced every other day at 22±2°C, and the relative humidity was 50%. The adaptive feeding was carried out for 7 days. The relevant operations and treatments involved in the experiment were approved and managed by the Experimental Animal Ethics and Use Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine.

Medicine used: catalpol (purity >90%, National Institute for the Control of Pharmaceutical and Biological Products, batch number: 2019-0819) and pentobarbital sodium (Tianjin Baishi Chemical Industry Co., Ltd., batch number: 160724). All testing kits were purchased from Nanjing Jiancheng Bioengineering Institute, including a urinary albumin (mALB) kit (batch number: 20190718), a urinary cystatin C (Cystain C) kit (batch number: 20190726), a urinary retinol binding protein 4 (RBP) kit (batch number: 20190803), a urine β2 microglobulin (β2-MG) kit (batch number: 20190912), a serum creatinine (Scr) kit (batch number: 2019-0804), a serum urea nitrogen (Bun) kit (batch number: 20190816), an angiotensin II (AngII) kit (batch number: 20190814), a serum arginine vasopressin (AVP) kit (batch number: 20-190816), and a serum endothelin (ET-1) kit (batch number: 20190902).

Other instruments we used included an intelligent non-invasive sphygmomanometer (China, Ruanlong Biotechnology Co., Ltd., BP 2006A), an automatic biochemical analyzer (Japan, Beckman, AU-480-10), a high-speed freezing centrifuge (Germany, Eppendorf, 5810R), and a full wavelength enzyme labeling instrument (USA, Thermo, Multiskan Mk3).

Experimental methods

Animal grouping and administration method: The SHR rats were randomly divided into 4 groups, namely, the SHR model group, the SHR + low-dose group, the SHR + middle-dose group, and the SHR + high-dose group. Healthy SPF rats were used as the control. The doses are listed below, with a low-dose of 10 $mg/kg{\cdot}d^{-1}$, a medium dose of 50 $mg/kg{\cdot}d^{-1}$, and a high-dose of 100 $mg/kg{\cdot}d^{-1}$. Saline solution was used as the vehicle. The selection of the drug dosages refers to Xu Shuyun's *Pharmacological Experimental Methodology*, and the equivalent dose was calculated according to the body surface area. The general state of the rats was observed daily, including their mental state, activity, hair, limbs, oral cavity, urination, reproductive orifice, their intake of food and water, and their urine and stools, to ensure the normal life activities of the rats.

Blood pressure measurement: The rats' tail artery pressures were measured using a US MRBP automatic non-invasive blood pressure measurement system on the day before the first drug administration, at 4 weeks after the first administration, and at 8 weeks after the first administration. In a quiet environment with appropriate humidity, the rats in an awake state were placed in a 37°C incubator that was preheated for 5-10 min. After the rats were completely quiet, a tail sleeve was placed on the tail root of each of the rats. The sleeve was automatically deflated after the pulse wave disappeared through automatic pneumatic compression. The first blood pressure waveform was systolic pressure. The blood pressure was measured six times at 30-second intervals, and the average pressure was calculated.

Urine sample collection and detection: The drug was administered for 8 weeks. Then the rats were placed in a metabolic cage, given normal drinking water and fasted, and kept for 24 hours. 24 hours of urine was collected, and the total urine volume was recorded. The samples were stored in -20°C freezer. In strict

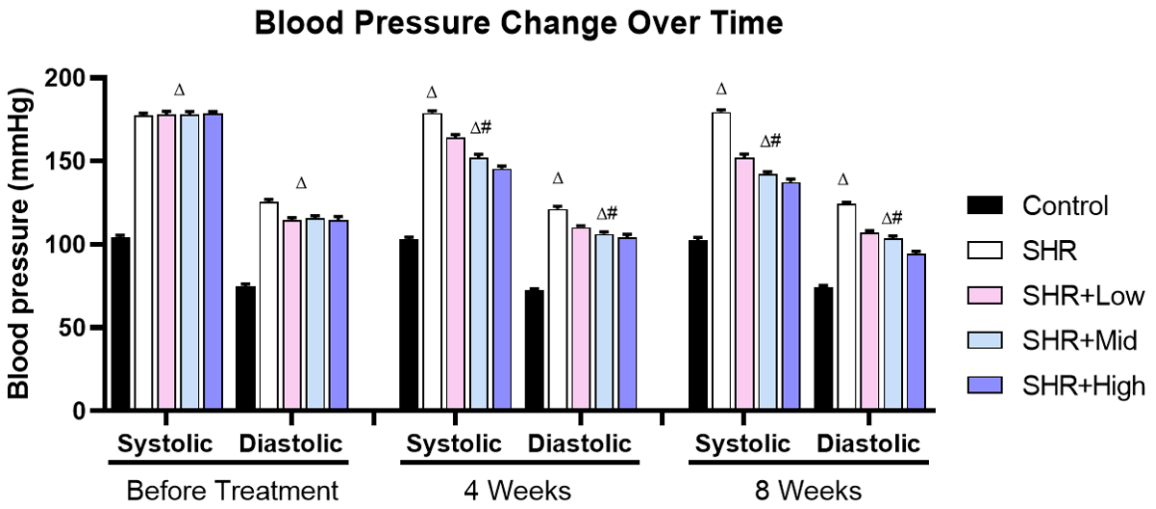

Figure 1. Changes in the systolic pressure and diastolic pressure of SHR rats affected by different doses of catalpol (x ± s, n=8). Differences compared with the control group, $^{\Delta}P<0.0001$; differences from inter compared with the SHR group comparisons, $^{\#}P<0.05$.

accordance with the kit instructions, the urine RBP, β2-MG, Cystatin C, and mALB levels were determined using an enzyme-linked immunosorbent assay.

Blood sample collection and measurement: After collecting their urine, each rat was weighed and anesthetized with 3% pentobarbital sodium (40 mg/kg). The abdominal cavity was opened, and the inferior vena cava was punctured with a 5 mL syringe to collect venous blood. The samples were kept on ice for 30 min, and centrifuged at 3000 r/min for 5 minutes at 4°C. The supernatant was collected and stored at -20°C before further analysis. The Scr and BUN levels were determined using an automatic biochemical analyzer. The serum AngII, AVP, and ET-1 levels were determined using an enzyme-linked immunosorbent assay. The specific operational steps were carried out strictly in accordance with the kit instructions.

Measurement of the right kidney mass index: After the serum collection, the organs were fully lavaged with 0.9% ice physiological saline until they turned white, and then the right kidneys were taken out and dried with filter paper to determine their weight, and then the right kidney mass index was calculated.

Statistical methods

The statistical analysis was performed using SPSS 22.0 statistical software. All the data are presented as the mean ± standard deviation (x ± SD). The comparisons among three or more groups were analyzed using one-way analysis of variance. The comparisons between two groups were carried out using Student's t-tests. P<0.05 indicated that a difference was statistically significant.

Results

Blood pressure

Before catalpol administration, the rats' systolic and diastolic blood pressure levels in each group were significantly higher than the levels in the control group (P<0.05), indicating the SHR model was reliable. After 4 and 8 weeks of administration, the systolic and diastolic blood pressure levels of the catalpol-treated rats decreased significantly in a dose-dependent manner compared to the SHR group (P<0.05). Higher dose catalpol treatments resulted in more significant decreases in the blood pressure levels. The blood pressure results are illustrated in **Figure 1**, and the actual systolic/diastolic pressure levels are listed in **Table 1**.

Urine indexes

The urine RBP, Cys-C, β2-MG, and mALB levels of all the catalpol treated rats decreased significantly compared to of the levels in the SHR rats (P<0.01). The decreases of the above in-

Table 1. The effects of different doses of catalpol on the systolic pressure and diastolic pressure in the SHR rats (x ± s, n=8)

Group	Before administration (mmHg)		4 weeks after administration (mmHg)		8 weeks after administration (mmHg)	
	Systolic pressure	Diastolic pressure	Systolic pressure	Diastolic pressure	Systolic pressure	Diastolic pressure
Control	104.16±1.45	74.83±1.46	103.21±1.15$^{\#}$	72.42±1.06$^{\#}$	102.43±1.84$^{\#}$	74.33±1.07$^{\#}$
SHR	177.42±1.31$^{\Delta}$	125.73±1.42$^{\Delta}$	178.87±1.43$^{\Delta,\#}$	121.32±1.64$^{\Delta,\#}$	179.34±1.49$^{\Delta,\#}$	124.26±1.05$^{\Delta,\#}$
SHR + Low	177.93±1.94*	114.64±1.43*	164.34±1.54$^{*,\#}$	110.17±1.07$^{*,\#}$	152.24±1.94$^{*,\#}$	107.26±1.06$^{*,\#}$
SHR + Mid	178.57±1.69*	115.56±1.74*	152.19±1.87$^{*,\#}$	106.23±1.34$^{*,\#}$	142.18±1.47$^{*,\#}$	103.53±1.62$^{*,\#}$
SHR + High	178.34±1.36*	114.76±1.93*	145.48±1.66$^{*,\#}$	104.35±1.65$^{*,\#}$	137.46±1.76$^{*,\#}$	94.34±1.54$^{*,\#}$
F	3556.608	1201.545	2707.466	1408.129	2107.561	1342.067
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: Differences compared with the control group, $^{\Delta}$P<0.0001; Differences from the intra group comparisons over time, *P<0.05; Differences from the inter group comparisons, $^{\#}$P<0.05.

Table 2. The effects of different doses of catalpol on the renal function and hypertension index in the SHR rats (x ± s, n=8)

Group	RBP (μg/L)	β2-MG (mg/L)	Cys-C (mg/L)	Malb (mg/L)
Control	85.78±24.3$^{\#}$	21.32±0.7$^{\#}$	0.20±0.11$^{\#}$	12.32±7.4$^{\#}$
SHR	131.38±31.2$^{\Delta,\#}$	59.01±14.7$^{\Delta,\#}$	0.48±0.16$^{\Delta,\#}$	70.03±24.6$^{\Delta,\#}$
SHR + Low	122.49±24.5$^{\#}$	46.29±14.2$^{\#}$	0.35±0.19$^{\#}$	53.98±17.1$^{\#}$
SHR + Mid	106.37±25.9$^{\#}$	38.19±10.7$^{\#}$	0.26±0.17$^{\#}$	39.42±9.5$^{\#}$
SHR + High	91.31±19.4$^{\#}$	34.12±12.4$^{\#}$	0.19±0.13$^{\#}$	14.35±3.4$^{\#}$
F	4.765	11.472	4.893	23.736
P value	0.004	<0.001	0.003	<0.001

Note: Differences compared with the control group, $^{\Delta}$P<0.0001; Differences from the inter group comparisons, $^{\#}$P<0.05.

Table 3. The effects of the different doses of catalpol on the biochemical indexes in the SHR rats (x ± s, n=8)

Group	Scr (μmol/L)	BUN (mmol/L)	AngII (ng/L)	AVP (ng/L)	ET-1 (pg/mL)
Control	23.75±16.3$^{\#}$	6.13±0.9$^{\#}$	5.21±0.4$^{\#}$	122.35±37.4$^{\#}$	103.12±25.4$^{\#}$
SHR	51.38±24.1$^{\Delta,\#}$	11.03±4.2$^{\Delta,\#}$	14.68±2.6$^{\Delta,\#}$	275.03±54.8$^{\Delta,\#}$	135.12±44.7$^{\Delta,\#}$
SHR + Low	42.64±18.5$^{\#}$	9.99±2.4$^{\#}$	12.32±3.3$^{\#}$	254.97±57.2$^{\#}$	103.78±43.9$^{\#}$
SHR + Mid	32.37±15.6$^{\#}$	8.09±1.9$^{\#}$	10.45±4.7$^{\#}$	235.72±35.5$^{\#}$	99.32±34.5$^{\#}$
SHR + High	21.31±8.5$^{\#}$	6.12±2.5$^{\#}$	7.5±1.9$^{\#}$	204.48±43.8$^{\#}$	91.72±29.6$^{\#}$
F	4.288	5.815	13.026	13.143	3.245
P value	0.006	0.001	<0.001	<0.001	0.003

Note: Differences compared with the control group, $^{\Delta}$P<0.0001; Differences from the inter group comparisons, $^{\#}$P<0.05.

dexes were dose-dependent (P<0.05). The results are shown in **Table 2**.

Serum indexes

The serum Scr, BUN, AngII, AVP, and ET-1 levels in the rats in the catalpol-treated groups were significantly decreased compared to the rats in the SHR group (P<0.01). With each dosage increase, the above indexes were significantly decreased (P<0.05). The results are shown in **Table 3**.

Right kidney mass index

After 8 weeks of treatment, compared with the healthy control rats, the right kidney mass index in the SHR rats was lower (P<0.05). The catalpol treatments increased the right kidney mass index significantly in a dose-dependent

Table 4. The effects of the different doses of catalpol on the right kidney mass index in the SHR rats (x ± s, n=8)

Group	Mass Index
Control	6.75±0.13#
SHR	3.34±0.12Δ,#
SHR + Low	4.04±0.05#
SHR + Mid	4.67±0.26#
SHR + High	5.41±0.82#
F	89.065
P value	<0.001

Note: Differences compared with the control group, ΔP<0.0001; Differences from the inter group comparisons, #P<0.05.

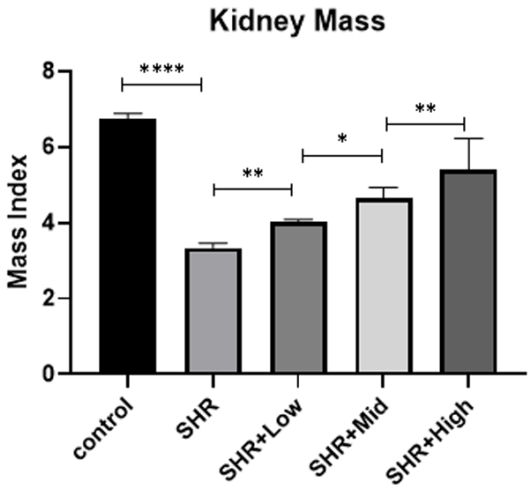

Figure 2. The effects of the different doses of catalpol on the right renal mass index of the SHR rats (x ± s, n=8). ****P<0.0001, **P<0.01, *P<0.05.

manner compared with the SHR group (P< 0.05). The results are shown in **Table 4** and **Figure 2**.

Discussion

Primary hypertensive nephropathy is renal damage caused by long-term hypertension, a condition that is often difficult to detect due to its lack of significant clinical manifestations. The symptoms of hypertensive nephropathy may include loss of appetite, nausea, fatigue, etc. The management of blood pressure is a lifelong commitment. Traditional Chinese medicine formulas have gained increasing attention in hypertension treatment due to their effectiveness and relatively low complication rates [5]. Herein, we used catalpol, a natural iridoid glucoside extracted from *Rehmannia glutinosa* Libosch to treat SHR rats in order to explore its antihypertensive and renal protective effects. The blood pressure and renal function parameters, including mALB, Scr, RBP, β2-MG, and Cystatin C were measured to evaluate the therapeutic effects of catalpol. We found the catalpol treatments significantly downregulated blood pressure in SHR rats after 4 weeks and 8 weeks of administration. And the renal function parameters were also impacted by the catalpol treatments.

mALB has a large molecular weight, and it is difficult for it to enter the urine through glomerular filtration under physiological conditions. In the early stage of hypertensive renal damage, the glomerular filtration barrier is destroyed, and the glomerulus is in a high filtration state, which increases the pressure in the capillaries, causing mALB to enter the urine. mALB is an early sensitive index for hypertensive renal damage [9, 10]. In our current study, we found catalpol treatments significantly decreased the mALB content in the SHR rats (P<0.05) in a dose-dependent manner, suggesting catalpol may protect the glomerular filtration barrier from damage and alleviate the proteinuria caused by hypertensive nephropathy. Cys-C can only be removed by the glomerular filtration barrier and excreted in the urine. This clearance method is not affected by factors such as exercise, muscle content, gender, or inflammation, and it is a sensitive index for diagnosing hypertensive renal damage [11, 12]. Herein, we found the Cys-C contents in the urine of catalpol-treated SHR rats were lower than the contents in the SHR rats (P<0.05), indicating that catalpol has a certain protective effect on glomerular filtration barrier damage caused by hypertension. β2-MG enters renal tubules through the glomerular filtration barrier, and the majority of β2-MG is reabsorbed in the proximal tubules. When hypertensive renal damage occurs and the renal tubular function is damaged, the β2-MG content in the urine may increase significantly and can be used as an early diagnostic marker for hypertensive renal damage [13]. In this study, we proved Catalpol reduced the urine β2-MG levels in SHR rats (as compared with the SHR control rats, P<0.05), and the higher the catalpol dose, the more significant the observed reduction effect (P<0.05). Therefore, catalpol also has a protective effect on renal tubular function in SHR rats. Physiologically, 90% of

RBP combines with the thyroid binding protein and cannot be filtered by the glomerulus, and 10% of the free RBP is reabsorbed by the proximal convoluted tubules after being filtered by the glomerulus, so the content of RBP in normal urine is extremely low [14]. Hypertension can lead to damage of the glomerular filtration barrier and renal tubular function, so the RBP content in the urine will increase [15]. We observed the RBP levels in the urine of SHR rats after the catalpol treatments were significantly lower than they were in the SHR rats ($P<0.05$), and the RBP levels were negatively correlated with the dose. It has been proved once again that catalpol has significant protective effects on the glomerular filtration barrier and the renal tubular function in SHR rats. The daily production of endogenous SCR is basically constant. When the intake of exogenous SCR is strictly controlled, the concentration of Scr is stable. Almost all Scr enters into the primary urine through glomerular filtration and is not reabsorbed by the renal tubules [16, 17]. Therefore, the measurement of Scr can reflect the glomerular filtration function. The results showed that the catalpol treatments significantly decreased the Scr levels in the SHR rats ($P<0.05$), and higher catalpol dosages resulted in a more significant downregulation of Scr ($P<0.05$). The BUN levels are associated with severe renal damage because it increases only when the glomerular filtration rate is decreased to 50% [18]. Catalpol significantly reduced the BUN level in the serum in SHR rats, and it was also inversely proportional to the dosage of catalpol ($P<0.05$). Therefore, the protective effect of catalpol on the kidneys of SHR rats is also reflected in the decrease of the serum Scr and BUN levels. AVP affects hemodynamic changes in the human body and aggravates renal function damage by activating distal tubules and V_2 receptors that collect ducts, so the AVP content can reflect the degree of renal function damage [19]. After catalpol treatment, the serum AVP levels in SHR rats is significantly decreased with the catalpol dosage, indicating the AVP level in the serum is also dose-related with catalpol. The significant activation of the renal RAAS system in hypertensive renal damage patients is an important pathological mechanism for the occurrence and progression of hypertensive renal damage [20]. The abnormal activation of the RAAS system initially results in an increase of AngII secretions, which causes the glomerular arterioles to contract significantly, aggravates glomerular hyperfiltration, damages the glomerular filtration barrier, and accelerates glomerular sclerosis. At the same time, it can also cause a renal inflammatory reaction, promote renal fibrosis, and eventually lead to serious renal damage. ET-1 is the strongest vasoconstrictor known so far. It binds to ET receptors, causing vasoconstriction and blood pressure elevation [21]. In addition, studies have shown that the ET-1 levels are closely related to the degree of renal damage [22, 23]. In this study, catalpol significantly reduced the serum AngII and ET-1 levels (both $P<0.05$ compared with SHR group) with a dosage correlation. Therefore, we demonstrated that catalpol can reduce blood pressure and protect kidney function by reducing the secretions of AngII and ET-1.

In summary, our results demonstrated catalpol has antihypertensive and renal protective effects on SHR rats in a dose-dependent manner. The urine RBP, Cys-C, β2-MG, and mALB levels and the serum Scr, BUN, AVP, AngII, and ET-1 levels in SHR rats after the intraperitoneal injection of catalpol are significantly reduced, suggesting catalpol can effectively attenuate renal damage caused by hypertension. So far, we found the high catalpol dosage we used did not present significant toxicity; however, a detailed toxicity study of catalpol will be our future focus. The molecular mechanism of catalpol-regulated hypertensive nephropathy will also be investigated in our future studies.

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Disclosure of conflict of interest

None.

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References

[1] Hart PD and Bakris GL. Hypertensive nephropathy: prevention and treatment recommenda-

tions. Expert Opin Pharmacother 2010; 11: 2675-2686.
[2] Kato T, Mizuguchi N and Ito A. Characteristics of podocyte injury in malignant hypertensive nephropathy of rats (MSHRSP/Kpo strain). Biomed Res 2015; 36: 313-321.
[3] Cui Y, Liu S, Cui W, Gao D, Zhou W and Luo P. Identification of potential biomarkers and therapeutic targets for human IgA nephropathy and hypertensive nephropathy by bioinformatics analysis. Mol Med Rep 2017; 16: 3087-3094.
[4] Álamo JM, Olivares C, Barrera L, Marín LM, Suarez G, Bernal C, Serrano J, Muntané J, Padillo FJ and Gómez MA. Conversion from calcineurin inhibitors to mTOR inhibitors stabilizes diabetic and hypertensive nephropathy after liver transplant. World J Transplant 2015; 5: 19-25.
[5] Xiong X, Yang X, Liu Y, Zhang Y, Wang P and Wang J. Chinese herbal formulas for treating hypertension in traditional Chinese medicine: perspective of modern science. Hypertens Res 2013; 36: 570-579.
[6] Leuenroth SJ, Okuhara D, Shotwell JD, Markowitz GS, Yu Z, Somlo S and Crews CM. Triptolide is a traditional Chinese medicine-derived inhibitor of polycystic kidney disease. Proc Natl Acad Sci U S A 2007; 104: 4389-4394.
[7] Yang T, Zheng Q, Wang S, Fang L, Liu L, Zhao H, Wang L and Fan Y. Effect of catalpol on remyelination through experimental autoimmune encephalomyelitis acting to promote Olig1 and Olig2 expressions in mice. BMC Complement Altern Med 2017; 17: 240.
[8] Zhu J, Chen X, Wang H and Yan Q. Catalpol protects mice against renal ischemia/reperfusion injury via suppressing PI3K/Akt-eNOS signaling and inflammation. Int J Clin Exp Med 2015; 8: 2038-44.
[9] Ding JC and Wang ZL. Clinical significance of joint detection of mALB and NAG for early kidney damage in burn patients. Minerva Chir 2015; 71: 168-172.
[10] Zhang J, Li N, Guo W, Ma C and Zhao G. Diagnostic value of urinary microalbumin level in postpartum acute kidney injury. Iran J Public Health 2018; 47: 367-372.
[11] Zhou J, Liu Y, Tang Y, Liu F, Zhang L, Zeng X, Feng Y, Tao Y, Yang L and Fu P. A comparison of RIFLE, AKIN, KDIGO, and Cys-C criteria for the definition of acute kidney injury in critically ill patients. Int Urol Nephrol 2016; 48: 125-132.
[12] El-Frargy MS, El-Refaey AM, Eid R and Hussien MA. Serum cystatin-C and BETA 2-microglobulin as accurate markers in the early diagnosis of kidney injury in neonates: a single center study. Saudi J Kidney Dis Transpl 2015; 26: 712.
[13] Cai XN, Wang CY, Cai Y and Peng F. Effects of renal denervation on blood-pressure response to hemorrhagic shock in spontaneously hypertensive rats. Chin J Traumatol 2018; 21: 293-300.
[14] Downes KJ, Dong M, Fukuda T, Clancy JP, Haffner C, Bennett MR, Vinks AA and Goldstein SL. Urinary kidney injury biomarkers and tobramycin clearance among children and young adults with cystic fibrosis: a population pharmacokinetic analysis. J Antimicrob Chemother 2016; 72: 254-260.
[15] Domingos MA, Moreira SR, Gomez L, Goulart A, Lotufo PA, Benseñor I and Titan S. Urinary retinol-binding protein: relationship to renal function and cardiovascular risk factors in chronic kidney disease. PLoS One 2016; 11: e0162782.
[16] Quan S, Pannu N, Wilson T, Ball C, Tan Z, Tonelli M, Hemmelgarn BR, Dixon E and James MT. Prognostic implications of adding urine output to serum creatinine measurements for staging of acute kidney injury after major surgery: a cohort study. Nephrol Dial Transplant 2016; 31: 2049-2056.
[17] Yang Y, Lang XB, Zhang P, Lv R, Wang YF and Chen JH. Remote ischemic preconditioning for prevention of acute kidney injury: a meta-analysis of randomized controlled trials. Am J Kidney Dis 2014; 64: 574-583.
[18] Lee J, Lee Y, Park B, Won S, Han JS and Heo NJ. Genome-wide association analysis identifies multiple loci associated with kidney disease-related traits in Korean populations. PLoS One 2018; 13: e0194044.
[19] Golembiewska E, Machowska A, Stenvinkel P and Lindholm B. Prognostic value of copeptin in chronic kidney disease: from general population to end-stage renal disease. Curr Protein Pept Sci 2017; 18: 1232-1243.
[20] Choi HY, Park HC and Ha SK. High water intake and progression of chronic kidney diseases. Electrolyte Blood Press 2015; 13: 46-51.
[21] Kowalczyk A, Kołodziejczyk M and Gorąca A. Nuclear factor κB inhibitor BAY 11-7082 suppresses oxidative stress induced by endothelin-1 (ET-1) in rat kidney. Postepy Hig Med Dosw (Online) 2015; 69: 1512-8.
[22] Hompesch C, Ma TW, Neyra JA, Ripley L, Xiao G, Inrig J, Toto R and Van Buren PN. Comparison of ambulatory blood pressure patterns in patients with intradialytic hypertension and hemodialysis controls. Kidney Blood Press Res 2016; 41: 240-9.
[23] de Cássia Mattos MR, Lemes HP and Ferreira-Filho SR. Correlation between pre- and post-dialysis blood pressure levels in hemodialysis patients with intradialytic hypertension. Int Urol Nephrol 2016; 48: 2095-2099.