

Mechanism of herbal medicine on hypertensive nephropathy (Review)

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Abstract. Hypertensive nephropathy is the most common complication of hypertension, and is one of the main causes of end-stage renal disease (ESRD) in numerous countries. The basic pathological feature of hypertensive nephropathy is arteriolosclerosis followed by renal parenchymal damage. The etiology of this disease is complex, and its pathogenesis is mainly associated with renal hemodynamic changes and vascular remodeling. Despite the increased knowledge on the pathogenesis of hypertensive nephropathy, the current clinical treatment methods are still not effective in preventing the development of the disease to ESRD. Herbal medicine, which is used to relieve symptoms, can improve hypertensive nephropathy through multiple targets. Since there are few clinical studies on the treatment of hypertensive nephropathy with herbal medicine, this article aims to review the progress on the basic research on the treatment of hypertensive nephropathy with herbal medicine, including regulation of the renin angiotensin system, inhibition of sympathetic excitation, antioxidant stress and anti-inflammatory protection of endothelial cells, and improvement of obesity-associated factors. Herbal medicine with different components plays a synergistic and multi-target role in the treatment of hypertensive nephropathy. The description of the mechanism of herbal medicine in the treatment of hypertensive nephropathy will contribute towards the progress of modern medicine.

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1. Introduction

The association between high blood pressure and the kidney is high (1,2). The kidney participates in the formation of blood pressure through the secretion of renin and the regulation of body fluids (3). The imbalance of such regulation leads to hypertension. In addition, the kidney is one of the important target organs affected by hypertension-associated damage (4,5). The renal tubules are sensitive to ischemia, and dysfunction of distal tubules concentration often occurs first, including increased nocturia, decreased urine-specific gravity and decreased urine osmotic pressure (6). Over time, proteinuria, mostly mild, may occur after glomerular ischemia, while moderate proteinuria may occur in certain patients with high blood pressure (7,8). The decrease in the glomerular filtration rate eventually leads to end-stage renal disease (ESRD). In terms of renal pathology, the kidney size is normal at the early stage, while the kidney volume is decreased at the late stage, and its surface is fine and granular. This is caused by arteriolosclerosis, which leads to renal parenchymal damage and ischemic sclerosis in certain glomeruli (9-11). Ischemic lesions are also found in the renal interstitium and tubules. In terms of treatment, the current therapeutic aim of modern medicine is only to protect the residual nephrons and to delay the progression of renal damage using antihypertensive drugs (2).

Herbal medicine has been historically used in the treatment of hypertensive nephropathy, and its clinical effect is remarkable. Therefore, it is of great clinical and economical importance to explore its mechanism of action. The present

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study aims to review the recent basic research on the mechanism of herbal medicine for the treatment of hypertensive nephropathy.

2. Pathogenesis of hypertensive nephropathy

Hypertensive nephropathy is more common in elderly patients >50 years of age with a long history of chronic hypertension, and is more prevalent in men compared with women (12). The clinical manifestations appear later than the pathological changes (13). Hypertension usually lasts for >10 years before the gradual emergence of nocturia, mild proteinuria and other associated clinical symptoms (14). This disease is usually preceded by distal tubular dysfunction, followed by glomerular dysfunction (15,16). The patient's renal pathology starts with renal arteriopathy, followed by ischemic renal parenchymal damage (11). Renal arteriosclerosis mainly affects the arterioles before the glomerulus, including hyaline degeneration of the glomerular arterioles, and thickening of the medium membrane of the interlobular and arcuate arteries (17,18). The reason for this is vascular endothelial damage and increased vascular cavity pressure, which results in the subcutaneous accumulation of plasma components (19,20). Hypertrophy and hyperplasia of membranous smooth muscle cells in the interlobular and arcuate arteries are accompanied by different degrees of intimal fibrosis (21). Both lesions lead to hardening and thickening of the arteriole walls, narrowing of the lumen and decreased renal blood supply, followed by ischemic renal parenchymal damage (22-24). As arteriopathy progresses, the glomerulus first undergoes ischemic shrinkage, namely capillary basement membrane wrinkling, while the lumen remains open. Next, ischemic sclerosis occurs, where the basement membrane is highly wrinkled and the capillary lumen collapses (25,26). The renal tubules and interstitium are also ischemic, including tubules atrophy, thickening of the basement membrane, interstitial fibrosis and limited mononuclear cell infiltration (27,28). When parts of the glomeruli are damaged, the remaining glomeruli compensatively enhance the discharge of metabolic waste substances, eventually leading to glomerulosclerosis.

The mechanisms of hypertensive nephropathy is mainly renal hemodynamic changes and vascular remodeling caused by hypertension (29,30). When hypertension occurs, changes in renal hemodynamics will lead to changes in the function and structure of renal arterioles, which is known as vascular remodeling (31). During hypertension, the change in arteriole function is mainly manifested as increased responsiveness to vasoconstrictive substances (32,33), which results in increased vascular resistance and decreased renal plasma flow. However, in previous studies, the renal function remained normal due to increased glomerular filtration fraction. If hypertension persists, it can lead to structural changes in renal arterioles, particularly in the interlobular and arcuate arteries, and to hypertrophy and proliferation of smooth muscle cells (34,35). The mechanism is complex, and is the result of various active substances in the circulation, as well as an imbalance of vascular endothelial synthesis and secretion. For example, endothelin-1 (ET-1) is increased, while nitric oxide (NO) is decreased (36-38). Finally, the renal arteriole wall thickens, the lumen narrows, the vascular compliance decreases, the renal plasma flow further decreases and the renal function is

damaged. However, not all the renal arterioles undergo hypertrophic remodeling, resulting in hypoperfusion and ischemic renal parenchymal damage. In fact, the arterioles in the other part of the kidney do not show hypertrophic remodeling, but rather compensatory hyperperfusion (39). The glomeruli, which are supplied by these arteries, also change from exhibiting hypertrophy to exhibiting focal segmental sclerosis (40). Although the purpose of hypertensive nephropathy treatment is to protect the residual nephron and delay the progression of renal damage, the key aim of the treatment is to effectively control blood pressure (4,9). Therefore, the majority of research on the treatment of hypertensive nephropathy focuses on hypertension. Moreover, relevant studies on the control and treatment of hypertensive nephropathy using traditional Chinese medicine via a variety of mechanisms also investigate hypertension (41-43). The basic studies on herbal medicine prescribed for hypertensive nephropathy are shown in Table I.

3. Mechanism of herbal medicine in the treatment of hypertensive nephropathy

Suppression of the renin-angiotensin system (RAS). The RAS plays an important role locally in the kidney. Angiotensin II (AngII) can directly bind to angiotensin receptors on renal arteriolar smooth muscle cells and stimulate vascular smooth muscle contraction (44). AngII also stimulates the sympathetic nerve to promote vascular smooth muscle resistance, thus leading to increased renal vascular resistance. In addition, AngII can increase sodium reabsorption through the aldosterone action on distal renal tubules, thus increasing the blood volume and leading to increased blood pressure (45). Numerous basic studies have shown that herbal medicine can play a crucial role in the treatment of hypertensive nephropathy by inhibiting RAS. Genipin, as one of the main components of *Gardenia*, can protect the renal function of spontaneously hypertensive rat (SHR) via the AngII-TLR/MyD88/mitogen activated protein kinase (MAPK) pathway (46). Qian Yang Yu Yin granules can suppress AngII in multiple manners. The mechanism includes alleviation of SHR and inhibition of 293T cells' effort induced by AngII through the epigenetic pathway associated with nicotinamide N-methyltransferase expression (47). The Jiangya Tongluo formula can regulate the protective effect of adrenomedullin and angiotensin in rats with hypertensive nephrosis (48). The heart-protecting musk pill can decrease the partial levels of AngII in SHR kidney, thus treating hypertensive nephropathy (49).

In addition to studies on hypertensive nephropathy, numerous studies have demonstrated that herbal medicine can show efficacy in the treatment of chronic kidney disease or hypertension by inhibiting the RAS. For example, *Chrysanthemum* acts as an antihypertensive by acting on the RAS (50). The water extracts of kidney bean sprouts have been demonstrated to inhibit angiotensin converting enzyme, thus exhibiting potential for lowering blood pressure (51). Alisol B 23 acetate, as one of the main ingredients of *Rhizoma alismatis*, can suppress the expression of constituents of the RAS, and can inhibit the epithelial-to-mesenchymal transition (EMT) in nephrectomised rats, thus lowering blood pressure, decreasing serum creatinine and preventing proteinuria (52). In addition, Alisol B 23 acetate can block the RAS/Wnt/ β -catenin axis

Table I. Basic experimental studies on herbal medicine prescriptions.

Composition	Animal	Cell	Mechanisms	(Refs)
Polygoni Multiflori Radix, Herba Bidentis Bipinnatae, Corni Fructus	-	293T cells	Suppression of renin-angiotensin system	(44)
Scrophulariae Radix, Alismatis Rhizoma, Cyathulae Radix	-	Human mesangial cells	Antioxidant stress and anti-inflammatory responses	(89)
Bidens pilosa Linn, Cornus officinalis Sieb. et Zucc, Fallopia multiflora (Tunb.) Harald., Scrophularia ningpoensis Hemsl., Cyathula officinalis Kuan, Alisma plantago-aquatica Linn.	SHR	-	Antioxidant stress and anti-inflammatory responses	(86)
Nacre, Cassia occidentalis, Safflower, Salvia miltiorrhiza, Chrysanthemum	SHR	-	Suppression of renin-angiotensin system	(45)
Artificial Mouchus, Cortex Cinnamomi, Calculus Bovis Artifactus, Styrax, Radix Ginseng, Syntheticum, Venenum Bufonis	SHR	-	Suppression of renin-angiotensin system; antioxidant stress and Borneolum anti-inflammatory responses	(46)

to improve podocyte injury and the EMT of HK-2 cells (53). Ergone, one of the main ingredients of *Polyporus umbellatus*, and pachymic acid B, one of the main ingredients of *Poria cocos*, have the same effect (53). In addition, poricoic acid ZA, ZF, ZG and ZH, which are important components of *Poria cocos*, inhibit the effect of the RAS to protect podocytes and renal tubular epithelial cells, but affect the RAS and the transforming growth factor- β 1 (TGF- β 1)/Smad axis (54,55). Previous studies have shown that poricoic acid ZC, ZD and ZE in *Poria Cocos* protect renal interstitial fibrosis due to unilateral ureteral obstruction in mice via TGF β /Smad pathway (56). It has been reported that 25-O-methylalisol F, the main component of *Alisma*, protects EMT of rat renal proximal tubular epithelial cell lines through this pathway (57). The therapeutic effect of *Radix Scrophulariae* on SHR can be attributed to the suppression of the RAS through the inhibition of the extracellular regulated protein kinase 1/2, c-Jun N-terminal kinase and p38 MAPK pathways (58). Xin-Ji-Er-Kang can inhibit oxidative stress by affecting the RAS, and can improve renal injury after myocardial infarction in rats (59). In addition, all herbal medicines that contain flavonoids, terpenoids, saponins and alkaloids are able to inhibit the RAS (16). Among them, common herbs containing flavonoids are *Scutellaria baicalensis*, *Flos cmysanthermi*, *Sambucus adnata* wall, bud of Chinese Scholar tree, *Equisetum* spp, *Chrysanthemum indicum* L., *Chamaecyparis obtusa*, *Orthosiphon stamineus* and *Tropaeolum Majus* L. (60-62). Common herbs containing terpenoids are the surface layer and sclerotium of *Poria cocos*, *Alismatis rhizome* and *Polyporus umbellatus* (56,60,63). A common herb containing saponins is the ginseng root (64). Common herbs containing alkaloids are *Gambirplant*, *leonurus*, *Ophora flavescens*, *S. subprostrata*, *S. alopecuroides* and *Uncaria rhynchophylla* (60,65,66).

Inhibition of sympathetic excitation. In patients with hypertension, the sympathetic adrenaline system is hyperactive from the central to the arterial walls. The synthesis and release of the neurotransmitter catecholamine increases, thus leading to renal arteriole contraction, and renal vascular resistance

increases, thus affecting vascular remodeling (67,68). In addition, the catecholamine released by sympathetic nerves can directly act on proximal renal tubules, and increase sodium reabsorption, blood volume and blood pressure (69,70). Although it has not been demonstrated yet that the mechanism of herbal medicine in the treatment of hypertensive nephropathy involves the regulation of the sympathetic nervous system, numerous herbal medicines have been reported to be able to play a role in the inhibition of sympathetic nervous system in previous basic experiments and clinical trials.

Chrysanthemum plays a role in decreasing blood pressure by inhibiting the sympathetic nerve (50). *Radix scrophulariae*, by inhibiting sympathetic excitement, suppresses SHR, and ventricular remodeling occurs (58). Astragaloside IV can decrease norepinephrine levels in the blood of high-fat diet-induced obese rats and in kidney tissues, which indirectly demonstrates that Astragaloside IV has the effect of inhibiting sympathetic nerves (71). Guizhi decoction can inhibit the cholinergic transdifferentiation of sympathetic nerves, and improve the anatomical and functional denervation of sympathetic nerves (72). In addition, acupuncture, electroacupuncture and moxibustion can also regulate the sympathetic nervous system, although their mechanism of action is complex (73-75).

Antioxidant stress and anti-inflammatory responses. Oxidative stress is caused by the imbalance of reactive oxygen species (ROS) and the antioxidant mechanism in the body. In hypertensive nephropathy, inflammatory damage is caused by the interaction of various cells such as macrophages and T lymphocytes, or inflammatory mediators or chemokines (13,76). These inflammatory cells secrete cytokines that can lead to endothelial dysfunction, which can aggravate and even lead to hypertension. Inflammatory reactions and oxidative stress play a common role and cause each other in hypertension-associated renal damage (77). Therefore, anti-oxidative stress and anti-inflammation can play a role in alleviating hypertensive nephropathy.

As the most widely used herb in cardiovascular diseases, *Salvia miltiorrhiza* can significantly improve SHR blood

pressure, decrease ROS production and improve vascular remodeling (78). The flower of *Coreopsis tinctoria* Nutt. is widely used in the treatment of hypertension, diabetes, obesity and other diseases. It exerts anti-inflammatory effects through its antioxidant stress properties and its ability to inhibit tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and nuclear factor- κ B (NF- κ B) (79). Brazilian red propolis could alleviate hypertension and kidney injury in 5/6 renal ablation model rats through antioxidant stress (80). As an extract of *Apocynum venetum*, its polyphenols can improve the renal index of D-galactose-induced oxidative stress in mouse models (81). *Tulbaghia violacea* can improve NF- κ B and TGF- β expression in Dahl salt-sensitive rat kidneys, and plays a role in lowering blood pressure and protecting renal function (82). Resveratrol, the main component of *Veratrum nigrum* L., has been demonstrated to have anti-ROS effects, and has the potential to lower blood pressure (83). As the main component of celery seeds, 3-n-butylphthalide plays a protective role in renal tubules through decreased stress, as well as the expression of pro-inflammatory cytokines and TGF- β 1 in kidney tissues (84). Resveratrol, the main component of *Veratrum nigrum* L., has been demonstrated to have anti-ROS effects, and has the potential to lower blood pressure (85). Paeonol can effectively improve the blood pressure of spontaneously hypertensive rats, and its mechanism may be associated with reduction of blood viscosity, antioxidant stress and improvement of antioxidant capacity (86). Galangin, as the main extract of *Alpinia officinarum hance*, inhibits ROS as well as the mRNA expression of prostaglandin-endoperoxide synthase 2, TNF- α , IL-1 β and IL-18, thus exerting a protective effect in rat renal epithelial cells (87). Icariin, as the main component of *Epimedium brevicornu*, can decrease the production of ROS by inhibiting the activity of NADPH oxidase, thus reducing the vasoconstriction effect of AngII-induced hypertension in rats (88). Natural antioxidants derived from food and herbal extracts such as tea polyphenols, curcumin and lycopene, have been widely used as complementary therapies to slow the progression of ESRD.

Jiang Ya Yi Shen granules exert their protective role by inhibiting NF- κ B signaling-mediated micro-inflammatory cytokines, including IL-6, TNF- α and intercellular cell adhesion molecule-1 (ICAM-1), on SHR nephropathy (89). Tongxinluo can inhibit the effects of oxidative stress and improve SHR glomerular sclerosis (90). Ban Xia Bai Zhu Tian Ma decoction could inhibit IL-1, IL-6, TNF- α and inducible nitric oxide synthase (NOS) in SHR to improve the heart damage caused by hypertension (91). Qian Yang Yu Yin granules can also inhibit the influence of AngII on the NADPH oxidase 4-dependent pathway, thereby inhibiting the proliferation of human mesangial cells, and lowering the production of ROS and anti-inflammatory response (92). The heart-protecting musk pill, also called Shexiang Baixin pill, can decrease TGF- β and ICAM-1, thus exerting an anti-inflammatory effect, and can be used to treat SHR nephropathy and to improve vascular remodeling (49,93). Xin-Ji-Er-Kang-induced NOS in high-salt induced hypertensive mice can improve the activity and oxidative stress, and alleviate vascular remodeling (94-96). Qingxuan Jiangya decoction can affect the TGF- β 1/Smad signaling pathway to play a crucial role in improving renal interstitial fibrosis

in SHR (97). In a previous study, Shengkang improved renal injury in mice with unilateral ureteral occlusion by acting on the TGF- β /Smad3, Sirtuin/forkhead box protein O and B-cell lymphoma-2-associated X protein pathways (98).

Regulation of vasoactive substances and other mechanisms of endothelial cell protection. Hypertension can promote the synthesis of endothelial cells and the secretion of a variety of vasoactive substances. These substances maintain vascular tension and permeability, but can lead to vascular smooth muscle hypertrophy and hyperplasia. The sustained effect of blood pressure on vascular endothelial cells will result in endothelial cell damage (99,100). In addition, the increase in endogenous plasma NO synthase inhibitors in patients affects the decrease in NO synthesis by endothelial cells (101). The increase in ET-1, which can lead to vasoconstriction, eventually leads to enhanced vasoconstriction response and increased renal vascular resistance, and promotes the occurrence of vascular remodeling (37). Therefore, the best indicator of endothelial cell function is observation of the dynamic changes in vasoactive factors such as NO and ET-1.

Cirsium japonicum improves the cardiac effects of renal hypertension in 2-kidney 1-clip rats by increasing serum NO levels (102). *Morinda citrifolia* can significantly decrease blood pressure and 24-h urinary NO metabolite in SHR, and its juice extract can increase the phosphorylation of endothelial NOS in human umbilical vein endothelial cells, and promote the endothelial vasodilation of the aortic ring and NO products in rats (103). *Zingiber officinale* var. *rubrum* exerts a significant vascular relaxation effect in SHR. Its possible mechanism of vasodilatation includes the release of NO or transmembrane calcium channels (104). Curcumin can protect the renal kidney function of cadmium-induced renal damage in rats, and can play a protective role on renal injury caused by hyperuricemia or high-fructose intake, and one of the mechanisms is to increase the production of NO (105,106). Morin (also known as 3,5,7,2',4'-pentahydroxyflavone) is widely present in fruits and vegetables such as almond, old fustic, Indian guava and Osage orange. This compound may play a strong role in vascular widening by NO, muscarinic receptors, β 2-adrenergic receptors and calcium channels (107). Hydroxysafflor yellow A, the principal component of *Carthamus tinctorius* L., induces angiogenesis in rat mesenteric arteries by transient receptor potential vanilloid 4 (TRPV4) -dependent calcium influx in endothelial cells (108). A large number of clinical experiments showed that sodium tanshinone IIA sulfonate combined with angiotensin receptor blockers (ARBs) had a stronger effect on improving renal function in patients with primary hypertensive nephropathy compared with ARB monotherapy (109). Sodium tanshinone IIA sulfonate, the main ingredient in the herb *Salvia miltiorrhiza*, has been shown to protect vascular endothelial cells. In addition, the combination of caffeic acid and ferulic acid can dilate blood vessels and resist ET-1, while exerting a hypotensive effect through ester bonds and telmisartan (110). Qingxuan Jiangya decoction can prevent hypertension and improve vascular remodeling in SHR by lowering the serum ET-1 level and inhibiting the TGF- β 1/Smad pathway (111). 17-Methoxyl-7-hydroxy-furanchalcone, as an active ingredient of *Fordia cauliflora*, was capable of improving cardiac reconstruction from hypertension in rats

by regulating the eNOS-NO signaling pathway (112). The combination of *Astragalus membranaceus* and *Salvia miltiorrhiza* can improve IL-1 β levels in SHR urine and eNOS levels in AngII-damaged human renal glomerular endothelial cells superfluid (113). San Cao decoction in network pharmacologic analysis may play a role in lowering blood pressure by regulating the PI3K-Akt-eNOS pathway (114).

Improvement of obesity-associated factors. Metabolic disorder is also an important cause of hypertensive nephropathy (115). Obesity plays a greater role than blood pressure in the progression of hypertensive kidney disease (116). Obesity itself is a risk factor for high blood pressure. And in obese patients, renal dysfunction and associated increased sodium reabsorption in renal tubules can lead to hypertension (117). The compression of perirenal fat on the kidneys results in the activation of RAS (117). Chronic obesity may gradually amplify hypertension, leading to resistance to antihypertensive treatment. (117). Insulin resistance leads to the constriction of the extruded arterioles, thus leading to high glomerular pressure, hyperperfusion and hyperfiltration (118,119). These studies have demonstrated that obesity is closely associated with the incidence of hypertensive nephropathy. Herbal medicine has unique advantages in improving obesity. Astragaloside IV, as one of the main ingredients of *Astragalus*, is used to treat hypertension in high-fat diet-induced obese rats due to its anti-inflammatory effect and its ability to improve leptin resistance (71). *Citrus paradisi* and *Ocimum sanctum* infusions can decrease blood pressure and protect kidney function in obese rats (120).

A number of studies have shown that Chinese herbs can improve the effects of obesity on the kidneys of patients. *Coptidis rhizoma* can lower the blood lipid level and renal weight of fat-prone rats, and can improve urinary protein creatinine ratio and creatinine clearance rate in rats (121). The mechanism may be associated with the inhibition of the NLRP3 inflammasome (121). Through treatment of obesity-associated glomerulopathy in model rats with *Tribulus terrestris* L., it was found that the herb could decrease the body weight, blood pressure, serum cystatin C levels and migration of rats, as well as improve human endothelial cells migration, thus protecting renal function (80). Curcumin, as one of the most important components of turmeric, can improve body weight, abdominal fat index, urinary protein excretion and average glomerular diameter in mice, and can protect podocytes from leptin damage by blocking the Wnt/ β -catenin pathway (122). At the formula level, Mai Tong Fang inhibits fat generation and triglyceride accumulation in 3T3-L1 adipocytes (123).

4. Model of hypertensive nephropathy in herbal medicine research

In hypertensive nephropathy, herbal medicine has significant clinical efficacy in relieving proteinuria and controlling the progression of renal injury. However, the number of studies on the treatment of hypertensive nephropathy with Chinese herbal medicine is limited (Table SI). As aforementioned, certain compounds can control and alleviate diseases from multiple perspectives, and the Chinese herbs that contain such compounds have been listed. Subsequently, the present review

tried to analyze the similarities of these plant medicines based on the theory of traditional Chinese medicine in an attempt to reach a conclusion. However, there are only few studies on this topic. Thus, the present review can only briefly discuss the summary of the application of herbal medicine in the basic research of hypertensive nephropathy.

In clinical research, the disease is often treated as one of the complications of hypertension, which has not received considerable attention. This is understandable, since the most effective way to control hypertensive nephropathy is to control blood pressure (124-126). Therefore, animal experimental models of hypertensive nephropathy are often used directly in hypertension models. Since hypertensive nephropathy is nephropathy caused by hypertension, modeling should ensure the presence of proteinuria without directly damaging the kidney. Therefore, the genetic hypertension model is the most common in such studies, while the renal hypertension model is the least desirable. Among these models, SHR was produced by inbreeding in Wistar rats with the highest blood pressure, and may progress to myocardial hypertrophy, heart failure, renal insufficiency and endothelium-dependent diastolic function impairment (127). Dahl salt-sensitive rats are SD rats on a high-salt diet (127). These rats showed myocardial hypertrophy, severe heart failure, hypertensive nephropathy, impaired endothelium-dependent diastolic function and other impairments (127-129). These animal models can reflect the pathogenesis of hypertensive nephropathy. Regarding cell models, previous studies have focused on endothelial cell injury, glomerular sclerosis and renal interstitial fibrosis (76). Therefore, the current common cell model involves the use of Ang II to interfere with endothelial cells and observe whether their function is abnormal, or to interfere with glomerular epithelial cells and renal tubular epithelial cells and observe whether they undergo EMT (54,130,131). The pathogenesis of hypertensive nephropathy is not only caused by an abnormal RAS, but is the result of multiple mechanisms. The best model would be extracting the serum of hypertensive animals or patients to incubate cells (132). However, no such model has been reported in the studies on herbal medicine for hypertensive nephropathy thus far. In future experimental cell research, such a model should be developed, so as to better reconstruct the patients' disease.

5. Discussion

This review summarized three points. Firstly, the pathogenesis of hypertensive nephropathy was summarized. Secondly, herbal medicine studies based on these mechanisms were listed. Thirdly, the shortcomings of the current basic research on hypertensive nephropathy models and areas for improvement were discussed.

Hypertension nephropathy is a relatively complex mechanism of nephropathy. The basic pathogenesis of this disease includes renal hemodynamic changes and vascular remodeling, which are caused by various etiologies. At present, the treatment of hypertensive nephropathy in modern medicine is concentrated at a single site or approach, but the curative effect is not ideal. Different components of herbal medicine have obvious advantages in the treatment of hypertensive nephropathy. Previous studies on the efficacy and mechanism

of herbal medicine in treating hypertensive nephropathy have suggested that herbal medicine plays an important role in improving renal perfusion, controlling vascular remodeling and delaying renal function progression. An interesting finding in these basic studies was that some herbs can act on two or three mechanisms at once. These experiments also provide evidence for the advantages of Chinese herbal medicine in the treatment of hypertensive nephropathy.

However, the clinical studies of herbal medicine on patients with hypertensive nephropathy are relatively scarce. Although basic research is essential in terms of the explanation of the mechanism, it is only used to observe the changes in a certain organ or even a certain type of cell, which makes the basic research itself somewhat static and one-sided, and it cannot observe the changes of patients dynamically and comprehensively as with clinical research. Therefore, basic research can only provide clues for the direction of clinical medicine, and cannot replace clinical research. Due to the lack of clinical data in this field, the content of this review has some limitations. In order to better promote traditional Chinese medicine, identify the efficacy of these herbs and explore their potential mechanisms, more clinical studies related to Chinese herbs are required in the future, as well as more well-designed, large-sample, long-term, randomized and controlled clinical trials to verify the efficacy and safety. With the in-depth study of herbal medicine, modern medicine will not only be able to treat hypertensive nephropathy, but also can make great progress in other disciplines.

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Availability of data and materials

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Authors' contributions

BL, HD and ZF provided valuable suggestions and guidance for writing this manuscript. ZD was responsible for collecting the majority of the material to be reviewed and for writing this manuscript. WL, YG and FL collected the rest of the material to be reviewed. ZZ, NZ and XD helped with writing the manuscript. QZ, XZ and JD were responsible for constructing Table 1. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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