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Research Progress on the Pharmacological Mechanism of Effective Components of Astragalus in Treating Kidney Diseases

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Abstract: ***Kidney disease, characterized by damage to kidney structure and function, is regarded as a major public health issue that endangers human health worldwide. Western medicine has certain limitations in the treatment of kidney diseases, whereas traditional Chinese medicine possesses unique advantages in treating kidney diseases due to its complex components acting on multiple targets and signaling pathways. Studies have found that polysaccharides, saponins, and flavonoids in the Chinese herbal medicine Astragalus membranaceus mainly target diabetic nephropathy, chronic renal failure, renal cancer, acute kidney injury, uric acid nephropathy, nephrotic syndrome, kidney stones, etc. Their mechanisms of action are related to inhibiting oxidative stress response, suppressing apoptosis, regulating autophagy, anti-renal fibrosis, inhibiting inflammatory response, improving cell pyroptosis, enhancing immunity, regulating endoplasmic reticulum stress, improving mitochondrial dysfunction, enhancing renal endothelial cell function, inhibiting mesangial cell proliferation, suppressing renal cancer cell migration, invasion, proliferation, and colony formation, inhibiting epithelial-mesenchymal transition of renal cancer cells, promoting apoptosis of renal cancer cells, suppressing macrophage inflammatory chemotaxis, reducing serum uric acid levels, regulating intestinal flora, improving calcium and phosphorus metabolism disorders, and regulating renal water and salt metabolism. Furthermore, research on the effective components of Astragalus membranaceus mainly focuses on Astragalus polysaccharides, astragaloside IV, calycosin, quercetin, etc., and is primarily conducted through animal or cell experiments. The relationship between multiple targets upstream and downstream of various signaling pathways, as well as the synergistic mechanisms between signaling pathways and active components, still require further investigation. This article aims to summarize the research progress on the pharmacological mechanisms of Astragalus membranaceus effective components in the treatment of kidney diseases both in vitro and in vivo, providing theoretical guidance for their further development and clinical application.***

Keywords: Kidney disease, Active components of astragalus, Astragalus polysaccharides, Astragaloside IV, Pharmacological effects, Research Progress.

1. Introduction

Kidney disease is a kind of disease characterized by renal structure and function damage [1]. It can be mainly divided into primary and secondary glomerular disease, renal tubular, renal interstitial, renal vascular disease, etc. clinically, chronic damage of the kidney is more common [2]. Research has found that over the past decade, due to changes in China's socioeconomic status, risk factors, healthcare, and environment, the prevalence of chronic kidney disease among Chinese adults has decreased from 10.8% to 8.2%. However, the awareness and control rates of chronic kidney disease and its complications remain low, and it has always been regarded as a major public health issue that endangers human health worldwide. Strengthening the prevention, treatment, and management of chronic kidney disease is of great significance for reducing the national disease burden [3]. Western medicine has certain limitations in the treatment of kidney diseases. Traditional Chinese medicine, with its unique advantage of complex components acting on multiple targets and multiple signaling pathways to treat kidney diseases, has gradually increased its registration volume in clinical trials, and the research content has also been continuously deepened [2,4]. Astragalus, one of the traditional Chinese medicines, is sweet in taste and mildly warm in nature. It possesses various therapeutic effects such as replenishing qi and raising yang, nourishing qi and strengthening the exterior, promoting diuresis and reducing swelling, generating body fluid and nourishing blood, removing stagnation and alleviating arthralgia, expelling toxins and promoting pus discharge, and astringing sores and promoting tissue regeneration. It is widely used in the treatment of various deficiency syndromes and chronic diseases. Currently, over 400 natural compounds have been isolated and identified from Astragalus, including its active ingredients such as astragalan, saponins, and flavonoids. In addition, it also contains various amino acids, trace elements, folic acid, coumarins, and betaine [5]. Modern pharmacological studies have shown that astragalus and its active ingredients have significant effects on anti-oxidation, anti-inflammation, anti-tumor, immune regulation, antiviral, anti-atherosclerosis, heart protection, liver protection, kidney protection, neuroprotection, anti-aging, anti-hypertension, and anti-hyperlipidemia [5,6]. At present, a large number of clinical practice and experimental studies have proved that the active ingredients of Astragalus can reduce proteinuria, improve renal function and improve renal histopathological changes, such as the thickening of glomerular basement membrane, the proliferation of glomerular membrane cells and the injury of endothelial cells, podocytes and renal tubular cells, which have been widely used in the treatment of various kidney diseases in clinic [7]. This article aims to summarize the advancements in research on the pharmacological mechanisms of Astragalus effective components in treating kidney diseases both in vitro and in vivo, thereby providing theoretical guidance for their further development and clinical application.

2. Diabetic Nephropathy

Diabetic nephropathy is a chronic kidney disease caused by

diabetes, characterized by glomerulosclerosis as the basic pathological feature, and is the main cause of end-stage renal disease. Studies have found that the active components of astragalus have been extensively researched in the treatment of diabetic nephropathy, which is of great significance for the clinical application of astragalus in the treatment of diabetic nephropathy.

2.1 Polysaccharides

Astragalus polysaccharide (APS) has the highest content and the strongest biological activity among the effective components of Astragalus. Xu Yanmei and other researchers found that APS can promote the expression of SIRT1 and inhibit the activation of erk1/2 and p38MAPK pathways, thereby inhibiting the oxidative stress and apoptosis of renal podocytes induced by high glucose [8]. Liu Xufeng and others found that APS can upregulate the transcription levels of AMPK, SIRT1, and FOXO1, as well as the phosphorylation level of AMPKα and the protein expression levels of SIRT1 and FOXO1 in renal tissues. It downregulates the phosphorylation and acetylation levels of FOXO1, activates autophagy by regulating the AMPK/SIRT1/FOXO1 signaling pathway, and inhibits oxidative stress response, thereby improving glucose and lipid metabolism and renal damage in diabetic nephropathy rats induced by a high-fat diet combined with streptozotocin [9]. It was found that APS could also inhibit gm41268/prlr pathway, reduce p62 and mTOR levels and increase LC3 ii/i ratio to restore autophagy, and downregulate FN, tgf- β and type IV collagen levels to alleviate renal fibrosis in diabetic nephropathy mice [10]. Wang Zuhua and others found that selenium-enriched astragalus polysaccharides can reduce the number of glomerular cells and extracellular matrix in streptozotocin-induced diabetic rats, increase E-cadherin expression, decrease α-SMA expression, delay or even reduce the transdifferentiation of renal tubular epithelial cells, thereby improving renal interstitial fibrosis [11]. Wu Dong and others found that astragalus polysaccharides can improve the levels of serum inflammatory factors in streptozotocin-induced diabetic nephropathy rats, reduce glomerular cell apoptosis, and enhance renal function by inhibiting the PI3K/AKT signaling pathway [12]. Wei Ruixian and others found that APS can regulate the expression level of SUR2B/Kir6.1 mRNA, promote the release of NO, and reduce the expression levels of NT protein, ET-1, and vWF in vascular endothelium to intervene in the NO-ONOO-oxidative stress pathway, thereby reducing stress damage, improving vascular endothelial damage in renal tissue of diabetic nephropathy mice, and protecting renal function [13]. Xu Xueyin discovered that APS may exert a protective effect on mitochondria by regulating the AMPK/SIRT1/PGC-1α pathway to maintain mitochondrial function and inhibit apoptosis mediated by the mitochondrial pathway, thereby enhancing the survival rate of renal tubular epithelial cells induced by high glucose [14]. Bao Fang and others found that astragalus polysaccharides can reverse the effect of high glucose on down-regulating Axin-1 and up-regulating β-catenin, leading to the inactivation of the Wnt signaling pathway and thus improving the apoptosis of renal tubular epithelial cells induced by high glucose [15]. In addition, Zhou Guangju and others found that Astragalus Polysaccharide Injection can also downregulate the levels of CXCL10, E-cadherin, and MMP-9 in patients with diabetic nephropathy, improve immune and inflammatory responses, thereby inhibiting renal interstitial fibrosis and mesangial matrix accumulation, and exerting a renal protective mechanism [16].

2.2 Saponins

2.2.1 Astragaloside IV

Astragaloside IV (AS-IV) is one of the main components of astragaloside extract, which has a variety of biological activities, and can be used as an important marker to evaluate the quality of Astragalus. At present, AS-IV is the most bioactive compound, which exerts a variety of pharmacological effects on important organs of the human body [17]. Li Yan and others found that AS-IV can improve glucose and lipid metabolism disorders and alleviate renal tissue damage in diabetic nephropathy rats by downregulating the expression of Caspase-1 and GSDMD in cell pyroptosis [18]. Wang Ruihua and others found that AS-IV can alleviate endoplasmic reticulum stress and inhibit inflammatory responses by regulating the IRE-1α signaling pathway and downregulating the expression of GRP78, IRE-1α, TRAF-2, and IKK-α, thereby exerting a protective effect on podocyte damage in diabetic nephropathy [19]. Huang Lixia and others found that AS-IV can promote the phosphorylation process of eNOS, increase the content of NO in the body, enhance vascular permeability and renal filtration, inhibit oxidative stress processes, and exert a protective effect on the kidneys of streptozotocin-induced diabetic nephropathy rats by regulating the eNOS/NO pathway, with the action site possibly being at Ser1177 [20]. Li Guoling and others found that AS-IV can activate the AMPK/eNOS signaling pathway, upregulate the gene expression of AMPK and eNOS in the kidney tissue of streptozotocin-induced diabetic nephropathy rats, promote the phosphorylation of AMPK and the protein expression of eNOS, thereby improving the function of renal endothelial cells [21]. Pei Xiang and others have found that AS-IV may exert a protective effect on renal damage in diabetic nephropathy mice by inhibiting excessive mitochondrial fission, promoting autophagy levels of damaged mitochondria, and enhancing the PINK1/Parkin signaling pathway [22]. Ma Keke and others also found that AS-IV may increase autophagy activity in renal tissue cells by inhibiting the PI3K/Akt/FoxO1 signaling pathway, thereby delaying the progression of diabetic nephropathy [23]. Yuanjihong and others found that AS-IV could regulate the nlrp3/caspase-1 pathway and significantly down regulate the expression of NLRP3, caspase-1 and TGF-β in renal tissue to inhibit renal interstitial fibrosis in diabetic nephropathy rats [24]. Song Gaofeng and others found that AS-IV inhibits the galectin-3/ERK1/2 signaling pathway, suppresses the proliferation of glomerular mesangial cells and the hyperplasia of extracellular matrix, thereby reducing proteinuria in streptozotocin-induced type 1 diabetic mice and protecting renal tissue [25].

2.2.2 Astragaloside I and Astragaloside II

Astragaloside I (ASI) and Astragaloside II (ASII) are also saponin compounds with representative activities extracted from the traditional Chinese medicine Astragalus

membranaceus. Duan Yafei and others found that Astragaloside I can upregulate the expression of Nephein protein and downregulate the levels of serum IL-1β, IL-18, as well as the expression of NLRP3, Cleaved-Caspase-1, and GSDMD-N proteins. It exerts an intervention effect on podocyte fusion and podocyte loss in diabetic kidney disease by inhibiting cell pyroptosis and improving podocyte damage [26]. Gao Chongting and others found that Astragaloside II could improve renal podocyte apoptosis, enhance podocyte adhesion, reduce podocyte shedding and play a renal protective role by downregulating the expression of Caspase-3 in renal tissue and upregulating the expression of podocyte related proteins nephrin and WT-1 in streptozotocin-induced diabetic nephropathy rats [27].

2.2.3 Isoastragaloside IV

Isoastragaloside IV is a monomer compound isolated from total astragaloside. Luan Zhongqiu found that isoastragaloside IV can improve the injury of human mesangial cells induced by high glucose by inhibiting cell proliferation, enhancing the antioxidant capacity of cells, reducing the production of reactive oxygen species, reducing the expression of tgf- β 1, Psmad2 / 3, NADPH Oxidase 4 protein, and increasing the expression of TRPC6 protein [28].

2.3 Flavonoids

As one of the active substances in Astragalus membranaceus, flavonoids have a variety of biological activities, mainly including calycosin isoflavones, formononetin, quercetin, isorhamnetin, kaempferol, etc., which can act on multiple targets to play its therapeutic role [5].

2.3.1 Calycosin

Nehal [29], Haidy [30] and others found that calycosin can reduce the levels of IL33/ST2 mRNA, decrease the contents of IL-1β, renal NF-κBp65, NLRP3, TXNIP, and MDA, increase the levels of IL-10 and TAC, as well as Nrf2 expression. By regulating the IL33/ST2 signaling pathway and the NF-κB/p65/NLRP3/TXNIP inflammasome signaling pathway, it can improve oxidative stress, inflammatory cytokines, and fibrosis processes in diabetic nephropathy rats, thereby delaying the progression of kidney disease.

2.3.2 Formononetin

Liu Fangwei and other researchers found that formononetin can reduce 24h urinary microalbumin, serum creatinine, serum urea nitrogen, apoptosis rate, RhoA, NOX4, rocl, eIF2 α, GRP78 levels, and inhibit endoplasmic reticulum stress injury and renal function in type 2 diabetic rats by regulating rho/rock/nox4 signaling pathway [31]. Zhang Xinyun and others found that formononetin could improve the renal function, blood glucose and lipid levels of streptozotocin-induced diabetic nephropathy rats, increase the activities of SOD and GSH Px, Nrf2 and HO-1 mRNA expression, nuclear protein Nrf2 and total protein HO-1 expression, and inhibit the oxidative stress response of renal tissue by activating nrf2/ho-1 signaling pathway [32]. Tian Xin and others discovered that formononetin inhibits the proliferation of high-glucose-induced glomerular mesangial cells by regulating the NF-κB signaling pathway, suppressing the protein phosphorylation levels of p65, IKKβ, and IκBα, as well as p65 nuclear translocation, and modulating the expression of inflammatory factors Mcp1, Csf1, Icam1, and Vcam1 mRNA [33].

2.3.3 Quercetin

Jiang Yifan and others found that quercetin can inhibit the HMGB1/RAGE/NF-κB inflammatory signaling pathway to improve kidney damage caused by diabetes. It can reduce the levels of inflammatory factors IL-1β, IL-6, and TNF-α, as well as the expression of HMGB1, RAGE, NF-κB, Bax, and Caspase-3, and increase the expression of Bcl-2, thereby alleviating renal inflammatory responses and inhibiting cell apoptosis [34]. Wang Xinghong and others found that quercetin can reduce the expression of P2X7R, NLRP3, ASC, Caspase-1, α-SMA, Collagen I, and Collagen III proteins. By regulating the renal P2X7R/NLRP3 signaling pathway, it inhibits inflammatory responses and renal fibrosis, thereby exerting a renal protective effect on diabetic nephropathy mice [35]. Zhao Haixia and others discovered that quercetin can decrease the expression of TGF-β, Smad2/3, α-SMA, and Snail in type 1 diabetic nephropathy rats, and promote the expression of E-cadherin, thereby inhibiting the occurrence and development of tubular epithelial-mesenchymal transition and renal interstitial fibrosis [36].

2.3.4 Kaempfero

Kaempferol is a common flavonoid, widely exists in a variety of vegetables, fruits and traditional Chinese herbal medicine, long-term diet can also reduce the risk of cancer. Tang Lihua and others found that kaempferol can improve the renal function and renal tissue damage of diabetes nephropathy rats, inhibit renal cell apoptosis and inflammatory reaction by reducing the expression of cl-cassase-3, cl-cassase-9, NLRP3, ASC and caspase-1, and the levels of inflammatory factors IL-18 and IL-1 β [37]. Xuan Lulu and others found that kaempferol can inhibit high glucose induced cell proliferation, ROS production, NOX activity, and MDA levels in glomerular mesangial cells, enhance intracellular SOD activity, inhibit the expression of TGF - β 1, Col IV, NOX4, and p22phox in cells, and increase the expression of Sestrin2 and AMPK cytokines. Its mechanism of action may be by regulating the AMPK/NOX4 signaling pathway to alleviate cellular oxidative stress response and extracellular matrix accumulation [38]. Chen Ni and others found that kaempferol could inhibit the upregulation of FN, CTGF mRNA, and protein expression levels in rat mesangial cells induced by high glucose, and inhibit the upregulation of p-p38MAPK protein expression in a dose-dependent manner. By regulating the p38 MAPK signaling pathway, it inhibited cell proliferation and thus protected the kidney [39]. Duan Bin et al. found that kaempferol can reduce the gene expression of NOX2 and NOX4 in human glomerular endothelial cells under high glucose conditions and inhibit the generation of ROS mediated by them. It can also enhance the function of the antioxidant pathway Nrf2/HO-1 and promote the clearance of ROS, thereby reducing oxidative stress response. It can also downregulate the expression of Bax and VDAC1 genes, upregulate the expression of HK-II and Bcl-2 genes, and inhibit the process of cell apoptosis by antagonizing the

mitochondrial apoptosis pathway [40]. Yu Xinlin and other researchers found that kaempferol can also enhance the proliferation and reduce the apoptosis rate of human renal epithelial cells induced by high glucose through inhibiting tgf-β 1/smad3 signaling pathway, and alleviate the process of renal fibrosis [41].

3. Chronic Renal Failure

Chronic renal failure refers to the progressive damage of renal parenchyma, which leads to the gradual atrophy of the kidney and the occurrence of renal fibrosis. It can rapidly progress to end-stage renal disease, increasing the burden of dialysis and reducing the quality of life of patients. Renal fibrosis is irreversible. How to delay the progression of renal failure and control renal fibrosis is of great significance to improve the prognosis of patients. Clinically, Astragalus is often used in combination with other Chinese herbs to delay the process of chronic renal failure, and its pharmacological research is also ongoing.

3.1 Astragalus Polysaccharides

Yang Jieke and others found that APS can regulate the lncRNA Arid2 IR/NF-κB signaling axis to regulate intestinal microbiota, repair intestinal barrier damage, maintain intestinal microbiota, and reduce renal burden, thereby playing a renal protective role in 5/6 nephrectomy induced chronic renal failure mice [42]. Zhang Hui and others found that APS can also inhibit the activation of TGF-β1/Smad/AP-1 pathway and suppress renal fibrosis in rats with chronic renal failure [43].

3.2 Astragaloside IV

You Yun and others found that AS-IV can reduce the average optical density and relative mRNA expression of Wnt4 and β - catenin proteins, thereby inhibiting the activation of the Wnt/β - catenin signaling pathway, improving calcium and phosphorus metabolism disorders in chronic renal failure rats, and alleviating kidney tissue damage [44]. Jiang Xuan and others found that AS-IV can downregulate α - SMA, TGF-β1, and p-Smad3 proteins, upregulate Smad7 protein, and inhibit the TGF-β1/Smads signaling pathway to alleviate renal fibrosis damage and improve renal function in rats with chronic renal failure [45]. Yang Ruqian and others found that AS-IV can improve renal tissue fibrosis in mice with unilateral ureteral ligation by inhibiting the protein expression of Toll/MyD88 dependent signaling pathway related factors (TLR4, TLR2, MyD88, TRAF-6, NF - κ B) and the release of terminal inflammatory factors TNF - α and IL-6 [46]. Liu Zhen and others found that AS-IV can activate the Nrf2/HO-1 pathway, thereby mediating the activation of the body's anti-inflammatory and antioxidant systems and exerting a protective effect on kidney damage in uremic rats [47].

3.3 Flavonoids

Hu and other researchers found that calycosin could inhibit autophagy and oxidative stress process in skeletal muscle atrophy of chronic kidney disease by regulating AMPK/SKP2/CARM1 signaling pathway, improve renal function and histopathological changes in 5/ 6 nephrectomized rats [48]. Hu and others found that calycosin pretreatment could significantly inhibit necroptosis and the expression of TGF-β1, TNF-α and TNFR1 by inhibiting the elevation of MLKL, RIPK1 and RIPK3. By inhibiting the necroptosis induced by TGF-β1/TNF-α/TNFR1 signaling pathway, they enhanced the anti renal fibrosis activity of bone marrow mesenchymal stem cells on TGF-β1-induced primary renal tubular epithelial cells and unilateral ureteral obstruction mice [49]. Liu Fang and other researchers found that calycosin could reduce the protein expression of ATF6, Bax, Caspase-3, chop and GRP78, increase Bcl-2 protein expression, and improve renal tissue injury and apoptosis in rats with chronic renal failure by regulating endoplasmic reticulum stress [50].

In addition, Chen Lasi and others found that formononetin could significantly reduce the expression of TGF-β1 and Smad3, and inhibit the progression of renal interstitial fibrosis in rats with unilateral ureteral obstruction by inhibiting TGF-β1/smad3 pathway [51]. Zhang Cui and others found that formononetin can also inhibit the protein expression levels of ASK1 and JNK in rats with unilateral ureteral obstruction, prevent cell apoptosis, and thus slow down the occurrence and development of obstructive nephropathy [52]. Li Yan and others found that high-dose quercetin could inhibit the relative expression of inflammatory factors TNF-α, IL-6 and fibrotic factors COL-1, FN and α-SMA mRNA in mice induced by unilateral ureteral ligation, reduce the expression of α-SMA and TGF-β1 in renal tissue, and improve the mesenchymal transition of renal tubular epithelial cells by down regulating the protein expression of α-SMA and TGF-β1, thus reducing the degree of fibrosis [53]. Guan Hongxiang and others found that isorhamnetin can improve renal function and renal pathological damage in rats with unilateral ureteral obstruction by inhibiting the expression of Snail1 protein. It significantly inhibits the deposition of renal interstitial collagen, increases the expression level of E-cadherin protein, thereby inhibiting the process of tubular epithelial mesenchymal transition and delaying renal interstitial fibrosis [54].

4. Renal Cancer

Renal cancer is a common malignant tumor in the urinary system, which is a heterogeneous tumor originating from renal tubular epithelial cells. At present, Western medicine treatment mainly includes radiotherapy, chemotherapy, surgery, arterial embolization therapy, and immunotherapy. However, due to factors such as tumor clinical stage, tumor location, and patient constitution, the clinical treatment effect is not significant, and the improvement of patient survival rate is not significant and there are many adverse reactions. The application of traditional Chinese medicine has improved the clinical symptoms and quality of life of kidney cancer patients, and significantly prolonged their survival time [55]. The traditional Chinese medicine differentiation of kidney cancer is mainly based on the combination of deficiency and excess, and Astragalus is one of the tonifying medicines that can enhance positive qi and resist evil, and is widely used in clinical practice.

4.1 Astragaloside IV

Shi Zhichao found that AS-IV can activate the Caspase pathway, inhibit the proliferation activity of renal cancer cells in a concentration dependent manner, produce cytotoxicity, promote ROS overexpression, reduce mitochondrial membrane potential, increase Caspase3/9 activity, and induce apoptosis of renal cancer cells [56]. Zou Zhaoyin and others found that AS-IV can reduce the activation of the SDF-1/CXCR4 signaling pathway, thereby inhibiting the proliferation and inducing apoptosis of the human renal adenocarcinoma cell line ACHN [57]. Zhang Yue and others found that AS-IV can regulate the miR-21 gene to inhibit the proliferation of renal cancer cells, promote cell apoptosis, and suppress the growth of renal cancer solid tumors [58].

4.2 Astragaloside II

Zhao Kai and others found that AS II can inhibit the migration and invasion ability of renal clear cell carcinoma cells, as well as cell proliferation and colony formation. This may be achieved by inhibiting the Wnt/β-catenin signaling pathway to suppress epithelial mesenchymal transition in renal cancer cells and inhibiting the phosphorylation of PI3K AKT mTOR signaling pathway to induce the expression of apoptosis executing protein cleved caspase-3, thereby achieving renal cancer cell apoptosis [59,60].

4.3 Flavonoids

Zhang and others found that calycosin reduced hyaluronic acid synthesis by downregulating HAS2 expression, further promoted the degradation of MAZ through the ubiquitin proteasome pathway, thereby regulating the MAZ/HAS2 signaling pathway to inhibit the proliferation, metastasis and progression of renal cell carcinoma. The study also found that calycosin also inhibited the proliferation and migration of renal cancer cells by up regulating the expression of miRNA-1246 and then blocking the CXCR4/ERK pathway [61]. In addition, Chen Xuancai and other researchers found that kaempferol can inhibit the cell proliferation, migration and invasion ability of renal clear cell carcinoma cells, and regulate the expression of e-cadherin/vimentin/n-cadherin protein by targeting the expression of bcl2a1, thereby inhibiting the epithelial mesenchymal transdifferentiation process of cancer cells [62].

5. Acute Kidney Injury

Acute kidney injury refers to the rapid decline of renal function in a short time due to various factors, mainly manifested by water, electrolyte, acid-base balance disorder, metabolite retention in the body, etc. The incidence of acute kidney injury is increasing year by year. Early detection and treatment can effectively reduce kidney injury, and even reverse or completely restore renal function. Clinically, drug-induced acute kidney injury is more common. Astragalus membranaceus has a protective effect on the kidney and can also be used as one of the potential drugs for the treatment of acute kidney injury.

5.1 Astragalus Polysaccharides

Wu Yongzhen and other researchers have found that Astragalus polysaccharide can inhibit the p38MAPK and erk1/2 signaling pathways by regulating the expression of vitamin D to inhibit the inflammatory response and apoptosis of renal tubular epithelial cells, so as to improve the injury of renal tubular epithelial cells caused by gentamicin and acute kidney injury in guinea pigs [63,64].

5.2 Astragaloside IV

Zhang Yuming and others found that AS-IV could activate SIRT1 signal, reduce the mRNA expression of pro-inflammatory factors IL-1β, IL-6, TNF-α and apoptosis related indicators Bax and Caspase-3 in kidney tissue, and also significantly reduce ROS production and MDA content, increase SOD and GSH content, thereby inhibiting the inflammatory response, oxidative stress and apoptosis in kidney tissue of mice with sepsis induced acute kidney injury [65].

5.3 Flavonoids

Wang and others found that calycosin could inhibit NF-κB signal activation and CCL2 expression stimulated by MIF, inhibit macrophage inflammatory chemotaxis mediated by MIF, and improve acute kidney injury caused by ischemia-reperfusion [66]. Zhang and other researchers found that calycosin can locally reduce renal injury, reduce NF-κB-mediated inflammatory response, increase PPARγ, and reduce EGR1 in a dose-dependent manner, indicating that it may inhibit NF-κB-mediated inflammation through PPARγ/EGR1 pathway, thereby reducing renal ischemia-reperfusion induced injury [67].

Hao Yan and other researchers found that formononetin can increase the mRNA expression of OPA1 and cytc and the protein expression of OPA1, mfn1 and cytc in rats with acute kidney injury induced by cisplatin, and reduce the mRNA expression and protein expression of drp1, p66Shc and caspase-9 and the content of ROS in renal tissue cells. It can inhibit the abnormal division of mitochondria, hinder the activation of p66Shc, reduce the release of cytc, avoid its binding with caspase9 precursor to activate Caspase3, so as to inhibit the generation of ROS and cell apoptosis, and protect renal tissue [68]. Zhou Haiyin and other researchers found that medium and high doses of formononetin can improve the renal function of sepsis induced acute kidney injury, increase the copy number of mitochondrial mtDNA in kidney tissue, significantly reduce ROS level and MDA content, significantly increase SOD activity and the mRNA and protein expression levels of SIRT1, PGC-1α, NRF-1, TFAM in kidney tissue. At the same time, EX527 intervention can significantly inhibit its improving effect on sepsis induced acute kidney injury, indicating that formononetin may improve kidney tissue mitochondrial biogenesis and inhibit mitochondrial oxidative stress injury by activating SIRT1/PGC-1α signaling pathway, thereby improving kidney tissue injury [69].

Studies have found that quercetin can reduce ROS levels, inhibit oxidative stress response, downregulate ATF3 expression, inhibit iron death, regulate multiple signaling pathways to reduce apoptosis and activate autophagy, protect kidney transplantation, etc [70]. Yang Haoruo and other researchers found that quercetin could up regulate the

expression of keap1/nrf2 signaling pathway, inhibit excessive inflammatory response, improve oxidative stress response, so as to alleviate the renal function and pathological damage of lipopolysaccharide induced acute kidney injury rats [71].

Isorhamnetin, as the primary metabolite of quercetin in the body, also has a certain therapeutic effect on kidney disease. Jia Jian and other researchers found that isorhamnetin can inhibit the expression of lncrna-gm33782 and its target protein CFH to reduce the inflammation and apoptosis of renal tubular cells in mice with acute kidney injury [72]. Qiu Shujuan and others found that isorhamnetin pretreatment could improve acute kidney injury induced by ischemia-reperfusion in rats by inhibiting the overactivation of NF-κB signal transduction system and oxidative stress process [73].

6. Other Kidney Diseases

Wang Xiaoliang and others found that AS-IV can inhibit the TIM-1 signaling pathway, increase the Th1/Th2 cell ratio, thereby suppressing the inflammatory response and reducing kidney damage in IgA nephropathy mice [74]. Zhan Gmingkang and others found that quercetin could up regulate the levels of rOAT3, rMRP4, rBCRP and rMATE1, promote the excretion of indoxyl sulfate and p-cresol sulfate, and reduce the level of serum uric acid, thereby improving renal injury in rats with uric acid nephropathy [75]. Studies have also found that quercetin can inhibit the formation of kidney stones and protect kidney function by exerting its powerful antioxidant damage function and affecting the expression of claudin protein to regulate renal water and salt metabolism [76]. Zhang Wangning and other researchers based on network pharmacology found that total flavonoids of Astragalus membranaceus have specific effects of multi-component, multi-target and multi-pathway, and can play a role in the treatment of nephrotic syndrome by regulating AGE-RAGE, PI3K/Akt, VEGF, IL-17, MAPK and other signaling pathways to regulate the process of inflammatory response, oxidative stress, apoptosis, autophagy and other biological processes [77].

7. Conclusion

There are various kinds of kidney diseases. There is no record of various kidney diseases in traditional Chinese medicine. Most of the clinical names are based on the clinical manifestations of kidney diseases, which can be classified into the categories of "edema", "kidney wind", "kidney fatigue", "scrofula", "drowning poison", "Guan Ge", etc. The kidney is the foundation of the five internal organs. If the five internal organs are ill for a long time, the kidney will be injured. Only when the kidney function is normal can it coordinate with the lung qi promotion and depression, and the spleen qi helping the fluid operation function to maintain the normal fluid distribution and excretion in the body. "Suwen · comment on Febrile Diseases" said: "the evil gathered together, its Qi will be empty.". Some doctors believe that the occurrence of kidney disease starts with the deficiency of kidney essence and Qi, and the five internal organs lose nourishment, then the lesions are clustered [78]. At present, many doctors believe that kidney diseases are mostly related to congenital deficiency, acquired disordered diet, overwork, emotional disorders and other etiologies. Often due to various chronic kidney diseases that persist for a long time, they can lead to spleen and kidney deficiency, lack of biochemical sources of Qi and blood, stagnation of water and dampness in the triple energizer, obstruction of Qi and blood circulation, resulting in deficiency, blood stasis, dampness, toxicity and other factors, which together lead to disease, and that the disease is fundamentally due to spleen and kidney deficiency [79]. Therefore, various kidney diseases are treated clinically by Invigorating the spleen and kidney. For those with deficiency of spleen and kidney qi, the dosage of Astragalus membranaceus should be paid special attention to. For those with large dosage, each dose can reach 120g [80]. It can be seen that Astragalus is widely welcomed in the treatment of kidney disease, and it is particularly important to study the pharmacological mechanism of its active ingredients in the treatment of kidney disease.

Astragalus membranaceus has various active ingredients and a wide range of pharmacological effects. This article fully shows the unique advantages of Astragalus membranaceus in the treatment of kidney disease by multi-target action and multiple signaling pathways. Studies have found that the active ingredients of Astragalus are mainly diabetes nephropathy, chronic renal failure, renal cancer, acute renal injury, uric acid nephropathy, nephrotic syndrome, kidney stones, etc. Its mechanism of action is to inhibit oxidative stress, inhibit apoptosis, regulate autophagy, resist renal fibrosis, inhibit inflammatory reaction, improve cell death, improve immunity, regulate endoplasmic reticulum stress, improve mitochondrial dysfunction, improve renal endothelial cell function, inhibit mesangial cell proliferation, inhibit migration, invasion, proliferation and colony formation of renal cancer cells, inhibit epithelial mesenchymal transformation of renal cancer cells, promote apoptosis of renal cancer cells, inhibit inflammatory chemotaxis of macrophages, reduce serum uric acid level, regulate intestinal flora, improve calcium and phosphorus metabolism disorders, and regulate kidney water and salt metabolism. At the same time, research on the active ingredients of Astragalus membranaceus mainly focuses on Astragalus polysaccharides, Astragaloside IV, Flavonoids, Quercetin, etc. In the future, further research is needed on the pharmacological mechanisms of other Astragalus saponins and flavonoids in the treatment of kidney diseases. In addition, the pharmacological research on the active ingredients of Astragalus membranaceus mainly focuses on animal or cell experiments, and the research level is relatively shallow. The research on the signal pathway mainly focuses on a single signal, and the mechanism of action of multiple targets in its upstream and downstream is unclear, as well as the synergy between the active ingredients. Therefore, further research on the relationship between the signal pathways and multiple targets in its upstream and downstream, as well as the synergy mechanism between the signal pathways and active ingredients is still needed in the future. In conclusion, Astragalus membranaceus, as a commonly used traditional Chinese medicine for the treatment of kidney disease, has broad prospects for the extraction of its effective components and the study of its therapeutic effect, which is worthy of further exploration.

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