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Modulation of MAPK Signaling Pathway by Traditional Chinese Medicine for the Treatment of Diabetic Renal Fibrosis

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Abstract: Diabetic nephropathy (DN) is one of the complications of diabetes mellitus, which has become an economic burden for human societies all over the world, and its progression may lead to renal fibrosis in later stages, altering the prognosis and quality of survival of diabetic patients. Numerous studies have shown that inflammation, oxidative stress, and endoplasmic reticulum stress promote the progression of renal fibrosis in diabetic nephropathy. Subject to the limitations of conventional Western medical treatment strategies, Chinese medicine has unique advantages in intervening diabetic renal fibrosis, and research on Chinese medicine monomers and compound formulas has made some progress so far, confirming that a variety of signaling pathways can delay the development of diabetic nephropathy and renal fibrosis, among which, the MAPK signaling pathway promotes inflammatory and fibrotic responses, and regulates the level of glucose and lipid metabolism. Experimental studies have shown that the treatment of DN by TCM may be realized through the MAPK signaling pathway. The article reviewed the regulatory mechanism of MAPK signaling pathway on DN and the progress of TCM monomers and TCM combinations in regulating the MAPK signaling pathway for the treatment of DN, with the aim of providing more theoretical basis for the research and development of TCM for the treatment of DN, and for the clinical use of medication.

1. Introduction

Diabetic kidney disease (DKD) is one of the microvascular complications of diabetes mellitus, and about 30% to 40% of diabetic patients may develop DKD, which is mainly characterized by persistent increase in urinary albumin excretion and/or progressive decrease in glomerular filtration rate, and ultimately develops into end-stage renal disease (ESRD) [1]. According to the survey, the prevalence of diabetes mellitus is continuously increasing, and the population of diabetes mellitus among adults (20-79 years old) in China is about 140 million, which is the first in the world [2]. The pathology of DN is characterized by the deposition of extracellular matrix (ECM) in glomerular and tubular

interstitium, which further leads to thickening of the endothelium of the renal vasculature and vitreous alterations, with glomerulosclerosis and renal mesangial fibrosis being the ultimate endpoints [3], which is also the cause of the progression of DN progresses to ESRD [4]. The pathogenesis is mainly a multifactorial effect of cytokines, inflammatory response, oxidative stress, epithelial mesenchymal transition, autophagy and other factors under the state of glucose-lipid metabolism disorders in the organism. Due to the low sensitivity of relevant targets to drugs, lack of specific diagnostic methods, there are fewer drugs targeting renal fibrosis, which is difficult to meet the clinical needs. There is an urgent need to further explore the pathogenesis of DN and develop targeted drugs. Traditional Chinese medicine (TCM), with its advantages of multi-component, multi-target, and multi-pathway synergistic effects, provides a new direction for the treatment of DN, and it can effectively slow down the progress of DN through evidence-based treatment, which has a high degree of acceptance in the patient group. Experimental studies have confirmed the efficacy of TCM in preventing and treating renal fibrosis in DN by regulating some signaling pathways. During the development of DN, the accumulation of ECM is accompanied by the reduction of renal intrinsic cells, which ultimately leads to glomerulosclerosis and renal tubular atrophy. mAPK is a protein kinase that includes three pathways: c-Jun amino-terminal kinase (JNK), extracellular regulated protein kinase (ERK), and p38. MAPK and regulates cellular activation of growth, proliferation, differentiation and apoptotic functions [5].

2. Overview of the MAPK signaling pathway

2.1. Structure of the MAPK signaling pathway

In eukaryotic cells, the MAPK signaling pathway family plays a vital role in regulating gene expression. It utilizes both transcriptional and non-transcriptional regulation in response to various external signals like hormones, neurotransmitters, growth factors, viruses, and stressful conditions. This pathway is involved in multiple cellular processes, such as growth, differentiation, migration, metabolism, and apoptosis. The MAPK pathway comprises three major kinases, which become activated and phosphorylated in a progressive manner downstream. These kinases are the MAPK kinase kinases, MAPK kinase, and mitochondria-activated protein kinase [6]. MAPKK kinase can be activated by upstream signaling proteins, leading to dual phosphorylation and activation of downstream MAPK kinases. The activated MAPKK phosphorylation cascade is then activated in the third layer, MAPK. Transcription factors in the cytoplasm or nucleus are phosphorylated and activated leading to the expression of target genes such as signals that mediate fibrosis Transduction in Fibrosis. Renal fibrosis in mice with kidney disease [7]. The most widely studied are the subfamilies of the MAPK signaling pathway: extracellular signal-regulated kinase 1/2 (ERK1/2); p38 MAPK; and c-Jun amino-terminal kinase (JNK, also known as stress-activated protein kinase-1 [SAPK1]).

2.1.1. Classical Pathway

Like many other protein kinases, activation of MAPKs requires phosphorylation on what is known as the "flexible ring." p38 MAPKs activate Thr-Gly-Tyr by dual phosphorylation. Threonine and tyrosine residues can be activated by the three bispecific MKKs/MAP2Ks (MAPK kinases) when appropriately stimulated. mKK6 phosphorylates four p38 MAPK family members are phosphorylated.MKK3 activates p38α, p38γ, and p38δ and does not activate p38β.MAP2Ks are activated by phosphorylation of two conserved serine/threonine sites on the activation loop. A number of MAP3Ks have been shown to trigger activation of p38MAPK, including ASK1 (apoptosis signal-regulated kinase 1), DLK1 (double leucine-streptokinase 1), TPL2 (tumor progression site 2), MLA

(tumor cells), MLK3 (mixed lineage kinase 3), MEKK (MAPK/ERK) and MEKK4, and serine/ threonine kinase-α shear isoform ZAK1 (leucine zipper and sterile-α).

2.1.2. Non-classical pathway

Another mechanism of p38 MAPK activation in T lymphocytes involves tyrosine phosphorylation of p38α, which is autophosphorylated on the activation loop, possibly in association with stimulation of proteins such as TAB1. Phosphorylation of p38α is phosphorylated on Tyr323 of the TCR proximal tyrosine kinase, ZAP70 (ζ-chain-associated protein kinase 70 k). ζ-chain-associated protein kinase 70 kDa) and p56lck, leading to the autophosphorylation of p38α and increasing its kinase activity on the substrate. gadd (growth arrest and DNA damage inducing protein) 45α, leading to the initiation of a three-tiered MAPK phosphorylation cascade. ask1 activates MKK4, which exclusively activates p38α, and MKK6, which preferentially phosphorylates p38β. p38MAPK phosphorylation of the substrate continues to elicit a variety of biological responses, including inflammation, apoptosis, proliferation, cell cycle regulation, and differentiation. (Figure 1)

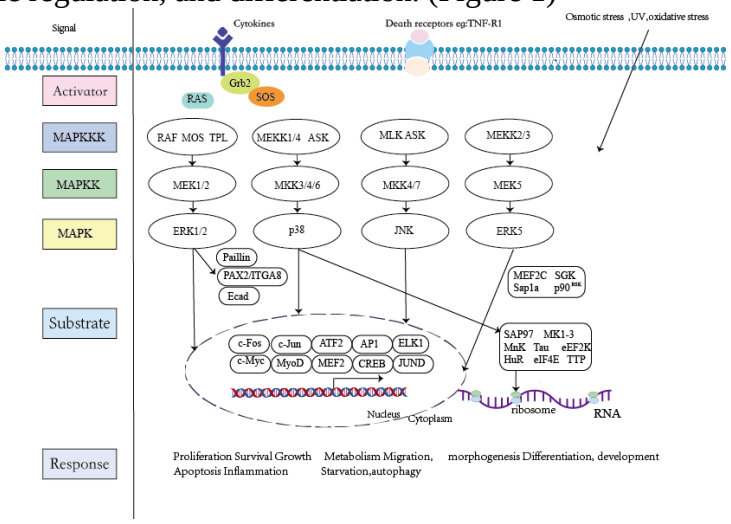

Figure 1: MAPK signaling pathway

2.2. ERK and JNK, as well as TGF-81 in renal fibrosis, activate the ERK pathway in podocytes

ERK and JNK and renal fibrosis TGF-81 activates the podocyte ERK pathway and induces metallo-matrix protease-9 expression, reducing ECM degradation. Inhibition of the long non-coding RNA ANRIL in high glucose-treated mouse thylakoid cells SV40-MES13 inhibits cell proliferation, inflammation and fibrosis by suppressing the Wnt/p-catenin and MEK/ERK pathways [8]. Overexpression of EphA1, a regulator of fibrosis, was reported to reduce phosphorylation of ERK1/2 and JNK and alleviate renal fibrosis in DN mice. Regulation of fibrogenesis by regulating renal mesangial cell proliferation and mesangial cell proliferation and ECM accumulation suggests a role for ERK MAPK in tubulointerstitial fibrosis. Extracellular signal-regulated kinases, p38 MAPK and JNK pathways play complementary roles in ECM deposition and fibrogenesis.

3. Traditional Chinese medicine based on MAPK signaling pathway for the treatment of DN renal fibrosis

3.1. Chinese medicine monomer

(1) Panax ginseng total saponin (PSN) is an active active ingredient extracted from Panax ginseng,

which has hemostatic, thrombolytic, anti-inflammatory, vascular repair, and immune-regulating effects, and it can reduce the progressive accumulation of ECM and anti-fibrosis in the kidneys. Sun Wen et al. [9] found that PNS had a protective effect on the kidneys of DN rats, and that PNS could ultimately regulate TGF-β1 protein and gene expression, P38MAPK phosphorylation, and Caspase-3 expression in renal tissues, and regulate TGF-β1, P38MAPK phosphorylation, reduce excretion of urinary proteins and Reduce oxidative stress, improve renal histopathological changes and protect renal function in DN rats.

(2) Yam polysaccharides Gao Zihan et al. [10] found that yam polysaccharides could reduce the expression of phosphorylated (p-)p38MAPK and downstream p-CREB protein in DN mice kidney tissue. nuclear transcription factor containing a kinase-inducible domain, could be activated by phosphorylated P38MAPK induction, reduce ECM deposition, decrease glomerular area and volume, thus reducing blood glucose and renal index, and slowing down the fibrosis of kidney tissue. The effect of this treatment is to reduce blood glucose and renal index and delay renal tissue fibrosis.

(3) Cordyceps sinensis Dong et al. [11] isolated a nucleoside/base enzyme-rich extract, CS-N, which was found to have therapeutic effects on diabetic renal fibrosis by inhibiting the p38/ERK signaling pathway and attenuating the deposition of EMT and ECM through experiments on DN mice, which may be related to adenosine and guanosine signaling.

(4) Curcumin Curcumin (Cur) is the main extracted component of the rhizome of Curcuma longa, which is known to activate blood circulation, promote blood circulation, move qi, and relieve pain. Among them, curcumin derivative J17 can reduce high glucose-induced inflammatory response, showing anti-inflammatory and antifibrotic active effects by inhibiting the activation of P38MAPK and Akt signaling [12]. Zhang Shaohua et al. found that curcumin reduced the expression levels of fibronectin, type IV collagen, TGF-β1, and p38MAPK in renal tissues of DN mice, and detected a decrease in renal function markers and apoptosis, suggesting that Cur may improve DN kidney injury.

(5) Ginsenoside Ginseng is sweet, slightly bitter, slightly warm in nature, and belongs to the spleen and lung meridians. It has the effects of tonifying vital energy, generating body fluid, quenching thirst, tonifying the spleen, benefiting the lungs, and calming the spirit and increasing intelligence. Its chemical composition is complex, and the current research focuses on ginsenosides and ginseng polysaccharides. Ren Dongwen [13] experimentally showed that imidazolepropionic acid (IMP, a harmful metabolite of intestinal flora) activates the Toll-like receptor 4 (TLR4) signaling pathway, causing inflammatory and fibrotic damage to renal cells.CK mainly relies on the inhibition of the TLR4-mediated NF-κB p65/TGF-β1 signaling pathway, the inhibition of ROS-mediated NLRP3 inflammasomes and the inhibition of NF-κB/p38 expression, thereby ameliorating renal injury in DN mice.

(6) Salvianolic acid B The main water-soluble component of the active ingredients of Salvia divinorum has anti-inflammatory, microcirculation improvement, and antioxidant effects. Zhu Yuanmei [14] found that the activation level of p38MAPK was significantly elevated under high glucose conditions in glomerular mesangial cells (HGMC), and Salvia divinorum B could significantly down-regulate its activation level and reduce the secretion of collagen and other extracellular matrices, and the degree of fibrosis in renal tissues of DN rats in the treatment group of Salvia divinorum B was reduced.

(7) Baicalein Scutellaria baicalensis has the effects of clearing heat and drying dampness, diarrhea and detoxification, and is commonly used in the treatment of fever and upper respiratory tract infections, etc. Baicalein belongs to the flavonoids, and is a specific inhibitor of p38MAPK. He, R., et al. [15] found that baicalein significantly reduced the expression of proteins, such as p38MAPK, p-p38MAPK, and NF-κB p65, etc., in glomerulus of diabetic rats, and improved the renal It was found that baicalein significantly reduced the expression of p38MAPK, p-p38MAPK and NF-κB p65 proteins in the glomeruli of diabetic rats, improved the renal pathological changes.

(8) Single herb Huangshuwai flower The main ingredient of Huangshuwai capsule is the extract of Huangshuwai flower, which has the effect of clearing heat and removing dampness, subduing swelling and detoxification; Mao Zhimin et al. [16] found that Huangshuwai capsule intervened in the unilateral nephrectomy combined with STZ to establish a rat model of DKD, and was able to down-regulate the renal tissue p38 MAPK signaling pathway conduction, inhibit the expression of p38 MAPK, TGF-β1, and TNF-α proteins , increase the anti-inflammatory and fibrosis level of renal tissue, inhibit renal fibrosis-related proteins and block the Klotho/TGF-β1/p38MAPK signaling pathway [17], and effectively improve DN. (Table 1)

Table 1: Traditional Chinese Medicine for Treating DN Renal Fibrosis

Form	Ingredient	Mechanism of action	Literatures
Chinese Medicine Monomers and Extracts	Panax ginseng total saponin (PSN)	Regulation of TGF-β1 protein and gene expression, P38MAPK phosphorylation, and caspase-3 expression in renal tissues	[9]
	yam polysaccharide	Downregulation of p38MAPK and downstream p-CREB protein expression reduces ECM deposition	[10]
	Cordyceps Sinensis (CS-N)	Inhibits p38/ERK signaling pathway, attenuates EMT and ECM deposition, associated with adenosine and guanosine signaling	[11]
	curcumin	Inhibition of P38MAPK and Akt signaling activation shows anti-inflammatory and anti-fibrotic activities	[12]
	ginsenoside	Inhibition of ROS-mediated expression of NLRP3 inflammasome and NF-κB/p38	[13]
	Salvianolic acid B	Down-regulates p38MAPK activation level and reduces extracellular matrix secretion such as collagen	[14]
	scutellarin	Reduced expression of p38MAPK, p-p38MAPK and NF-κB p65 proteins	[15]
medicine made from a single herb	yellow marshmallow flower (Liquidambar formosana)	Inhibition of p38 MAPK, TGF-β1 and TNF-α protein expression	[17]
a compound prescription of Chinese medicine	Fushengongfang	Reduced collagen deposition and activated expression of p38 MAPK protein molecule in renal interstitium	[18]
	Tongxinluo	Down-regulation of TGF-β1, P-p38 MAPK, FN and Col-IV protein expression levels in renal tissues	[19]
	Sugar Nephropin Capsules	TGF-β1/p38 MAPK signaling pathway transduction, Caspase-3 mRNA and protein expression levels, reduced MDA factor levels, and promoted NO and SOD factor expression	[20]
	Danhong Huayu Oral Liquid	Reduction of TGF-β1, p38MAPK, and Caspase-3 mRNA expression levels and reduction of collagen fibers in renal interstitial inflammatory cells	[21]
	Tonifying Kidney and Promoting Blood Soup	Downregulation of Ras-associated C3 botulinum toxin substrate 1 (Rac1)/p21-activated kinase 1 (PAK1)/p38 MAPK signaling pathway and decreased expression of downstream factor alpha-SMA and fibroblast-specific protein-1 (FSP-1)	[22]
	Radix Astragali Di Sugar Kidney Granules	Down-regulation of serine 307 (Ser307)/tyrosine 896 (Tyr896) phosphorylated expression of insulin receptor substrate-1 (IRS-1), (PI3K)/(Akt) signaling pathway transduction	[23]
	Urotica Granules	Upregulation of NO levels and inhibition of p38MAPK, Caspase-3 signaling pathway through downregulation of TGF-β1 expression	[24]

3.2. A compound prescription of Chinese medicine

(1) Fushengongfang The clinical experience of National Medical Master Prof. Guo Ziguang's formula, Fukui Kung Fang [18], has been shown to reduce the activity of p38 MAPK and TGF-β1 signaling pathway, reduce pro-inflammatory and pro-fibrotic factors, and delay the degree of renal damage in CRF; renal mesangial collagen deposition and pp38 MAPK protein expression were significantly reduced after treatment in the model group.

(2) Tongxinluo The formula is as follows: ginseng, leech, cicadas, earthworm, whole scorpion, centipede, red peony; Tong Yu et al. [19] confirmed that Tongxinluo has a protective effect on DKD, and Tongxinluo was able to down-regulate the expression level of TGF-β1, P-p38 MAPK, FN, and Col-IV proteins in the renal tissues, which improves the level of renal antifibrotic in rats with DKD, and attenuates the renal injury in DKD.

(3) Sugar Nephropin capsule Ugdunqiqi et al. [20] showed that DN rats treated with sugar nephropin capsule reduced renal pathological injury, and reduced renal injury due to oxidative stress and apoptosis by regulating the renal tissue TGF-β1/p38 MAPK signaling pathway conduction, Caspase-3 mRNA and protein expression levels, reducing the level of MDA factor, and promoting the expression of NO and SOD factors.

(4) Dan Hong Huayu Oral Liquid is composed of Salvia miltiorrhiza, Angelica sinensis, safflower, Chaihu, Rhizoma Ligustici Chuanxiong, peach kernel and Citrus aurantium, which can activate blood circulation and eliminate blood stasis, move qi and clear the channels. Qin Wenmin et al. [21] showed that the expression levels of TGF-β1, p38MAPK, and Caspase-3 mRNA were significantly reduced, and there were fewer renal interstitial inflammatory cells and collagen fibers. Danhong Huayu Oral Liquid may protect DN rat kidney by regulating renal TGF-β1, p38MAPK, Caspase-3 mRNA expression.

(5) Kidney Tonifying and Blood Activating Decoction Consisting of tonifying bone marrow, Myrrh. Wang et al. [22]. In a DKD mouse model, found that tonifying kidney and activating blood soup could down-regulate the transduction of Ras-related C3 botulinum toxin substrate 1 (Rac1)/p21-activated kinase 1 (PAK1)/p38 MAPK signaling pathway and reduce the expression of downstream factor α-SMA and fibroblast-specific protein-1 (FSP-1), inhibited podocyte epithelial EMT, and ameliorated renal pathological injury.

(6) Astragali Di Sugar Kidney Granules are composed of Astragalus, Radix Di Huang, Fructus Gorgonzola, Cornus officinalis, Leeches, Rhubarb, and Cnidium albidum; Gao et al. [23] confirmed that Astragali Di Sugar Kidney Granules inhibited the transduction of ERK/p38 MAPK signaling pathway through the DKD mouse animal model experiment, and down-regulated the expression of Ser307/tyrosine 896 of Insulin Receptor Substrate-1 (IRS-1) (Tyr896) phosphorylation expression, activate the downstream pathway phosphatidylinositol 3-kinase (PI3K)/protein kinase (Akt) signaling pathway, reduce renal insulin resistance, reduce proteinuria, improve renal pathological injury, and protect renal function in DKD mice.

(7) Uremic Clear Granules It is composed of rhubarb, atractylodes, astragalus, Prepared He Shou Wu, Rhizoma Ligustici Chuanxiong, Salviae Miltiorrhizae, licorice, ginger semilobatae, Citrus aurantium, Poria cocos, and chrysanthemum. Zeng Wenying et al. [24] found that urethane clear granules can significantly reduce the levels of urinary protein, blood creatinine, urea nitrogen, up-regulate the level of NO, alleviate glomerular and tubular injuries, renal fibrosis, alleviate oxidative stress as well as podocyte apoptosis by down-regulating the expression of TGF-β1 and inhibiting the signaling pathway of p38MAPK and Caspase-3.

4. Conclusion and outlook

In summary, studies have confirmed that many traditional Chinese medicines and Chinese herbal

compounds exert anti-oxidative stress, anti-fibrosis and other effects through the transduction of MAPK signaling pathway, which are closely related to the pathological process of DN, and are an important direction for the treatment of DN by traditional Chinese medicine. However, there are still many shortcomings in the study of Chinese medicine intervention in MAPK signaling pathway to improve DN renal fibrosis: (1) Chinese medicine compound composition is diverse, there is still a lack of experimental research to verify the interaction mechanism and the target of the action of the specific active ingredients, and the mechanism of pharmacotoxicity and pharmacokinetics of the active ingredients of the Chinese medicine needs to be clarified. (2) The intervention of traditional Chinese medicine is mainly based on in vitro modeling studies, lacking clinical data support and evidence-based medical verification. The research on MAPK signaling pathway is mostly limited to p38MAPK and JNK signaling pathway, and the research on other pathways is reduced. In conclusion, although there are some limitations in the study of TCM to prevent and control diabetic renal fibrosis through MAPK signaling pathway, it still provides a new direction for delaying DN renal fibrosis.

References

[1] Van Buren P N, Toto R. Current update in the management of diabetic nephropathy [J].Curr Diabetes Rev, 2013, 9(1):62-77.

[2] Zhang Zhirong, Han Weixia, Wang Chen. New progress on the molecular mechanism of diabetic nephropathy [J]. Chinese Electronic Journal of Nephrology, 2021, 10(2): 90.

[3] Endocrinology and Metabolic Diseases Professional Committee of Integrated Traditional Chinese and Western Medicine Physicians Branch of Chinese Medical Doctor Association, Yu Jiangyi, Ni Qing, Liu Su. Clinical Guidelines for the Prevention and Treatment of Diabetic Kidney Disease in China [J]. Journal of Traditional Chinese Medicine, 2022, 63(2):190-197.

[4] Gao Yanbin, Liu Tonghua, Nan Zheng, et al. Chinese medicine diagnosis and treatment standard of diabetic kidney disease [J]. World Journal of Integrative Medicine, 2011, 6(6): 548.

[5] Sun H, Saeedi P, Karuranga S et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045[J]. Diabetes Research and Clinical Practice, 2022, 183:109119.

[6] Liang Yajing, Yang Wanxi. Kinesins in the MAPK cascade: how kinesin motors are involved in the MAPK pathway? [J]. Gene, 2019(5):684:1-9.

[7] Li Zhenzhen, Liu Xianghua, Wang Baoying, et al. Pirfenidone suppresses MAPK signalling pathway to reverse epithelial-mesenchymal transition and renal fibrosis [J]. Nephrology (Carlton) 2017, 22(8):589-597.

[8] Fang Xun, Hu Jun, Zhou Hongyan. Knock-Down of Long Non-Coding RNA ANRIL Suppresses Mouse Mesangial Cell Proliferation, Fibrosis, Inflammation via Regulating Wnt/β-Catenin and MEK/ERK Pathways in Diabetic Nephropathy [J]. Experimental and clinical endocrinology & diabetes: official journal, German Society of Endocrinology [and] German Diabetes Association, 2020, 130(1).

[9] Sun Wen. Experimental study on the renoprotective effect of total saponins of Panax ginseng on the kidney of rats with diabetic nephropathy and its effect on TGF-β1/p38MAPK signaling pathway[D]. Beijing University of Traditional Chinese Medicine, 2010.

[10] Gao Zihan, Li Ruifang, Lu Xingzhi, et al. Effects of yam polysaccharide on renal function and aldose reductase pathway in mice with diabetic nephropathy [J]. Chinese herbal medicine, 2019, 42(3):643-646.

[11] Dong Zhonghua, Sun Yueyue, Wei Guangwei, et al. A Nucleoside/Nucleobase-Rich Extract fromCordyceps Sinensis Inhibits the Epithelial-Mesenchymal Transition and Protectsagainst Renal Fibrosis in Diabetic Nephropathy [J]. Molecules, 2019, 24(22): 4119.

[12] Chen Hongjin, Yang Xi, Lu Kongqin, et al. Inhibition of high glucose-induced inflammation andfibrosis by a novel curcumin derivative prevents renal and heart injury in diabeticmice [J]. Toxicology letters, 2017, 278:48-58.

[13] Ren Dongwen. Study on the effect of ginsenoside Compound K in the treatment of diabetic kidney disease and its mechanism [D]. Tianjin University of Traditional Chinese Medicine, 2022.

[14] Zhu Yuanmei. Study on the ameliorative effect and mechanism of salvinorin B on diabetic renal fibrosis [D]. Anhui South Medical College, 2019.

[15] He Riming, Men Ling, Yi Wuyong, Yi Tigang, Li Shunmin, Yang Shudong. Effect of baicalein on p38MAPK expression in renal tissues of rats with diabetic nephropathy [J]. Guangdong Medicine, 2016, 37(20):3006-3009.

[16] Mao Zhimin, Wan Yigang, Sun Wei, Chen Haoli, Huang Yanru, Shi Ximiao, Yao Jian. Role and mechanism of inhibition of oxidative stress and p38MAPK signaling pathway activity in renal tissues of diabetic nephropathy to improve renal fibrosis by Huang Kui capsule [J]. Chinese Journal of Traditional Chinese Medicine, 2014, 39(21):4110-4117.

[17] Gu Liyuan, Sun Yun, Tang Haitao, Xu Zhengxin, et al. Huangkui capsulei 1 combination with metformin amelforates diabetic nephropathy via the KIotho/TGF-B 1/p38MAPK sign aling pathwaylul [J]. Ethnopharmacol, 2021, 281:113548.
[18] Tong Pan, Huang Xuekuan, Shen Qing, et al. Effects of Fukui Kung Fang on p38 MAPK signaling pathway in rats with chronic renal failure [J]. Chinese Journal of Experimental Formulas, 2020, 26(14):105-110.
[19] Tong Yu, Gao Yanbin, Wang Xiaolei, Tian Nianxiu, Geng Jianguo. Tongxinluo regulates p38 MAPK pathway to inhibit extracellular matrix deposition [J]. Global Chinese Medicine, 2017, 10(02):146-150.
[20] Wugedunqiqige, Zhao Zongjiang, Jiang Yufeng, Yang Meijuan, Zhang Xinxue, Zhang Xiaomei, Du Lei. Protectory effects of Tang Shen Ping Capsule on kidneys in STZ-induced diabetic nephropathy rats and TGF-β_1/p38MAPK signal pathway [J]. China Journal of Traditional Chinese Medicine and Pharmacy, 2012, 27(04):1092-1097+1220-1221.
[21] Qin Wenmin, Zhou Caihong, Yang Kerang. Effects of Danhong Huayu oral solution on rats with diabetic nephropathy [J]. Journal of Chinese Medicinal Materials, 2016, 39(09):2114-2117.
[22] Yu Xiang. The effect of Tongfang Drainage Formula on renal fibrosis and TGF-β1/p38MAPK pathway in rats with chronic kidney disease [D]. Nanjing University of Traditional Chinese Medicine, 2019.
[23] Gao Xue, Liu Hongfang, An Zhichao, He Qiying. QiDiTangShen Granules Reduced Diabetic Kidney Injury by Regulating the Phosphorylation Balance of the Tyrosine and Serine Residues of Insulin Receptor Substrate 1 [J]. Evidence-based Complementary and Alternative Medicine, 2018:1-12.
[24] Zeng Wenying, Xin Chuanwei, Yu Xiali, Xia Zhongni. Effects of thirst-quenching combination on the expression of P38MAPK-FN in renal tissues of db/db mice [J]. China Traditional Chinese Medicine Science and Technology, 2020, 27(02):183-185.