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Research Progress of Traditional Chinese Medicine in Regulating Signaling Pathways of Kidney Fibrosis

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Abstract: ***Renal fibrosis is one of the important pathological changes in the progression of chronic kidney disease (CKD), and its progression rate directly determines the degree of renal function loss, which is closely related to the progression of CKD. Therefore, delaying the progression of renal fibrosis is essential to preserve kidney function. Studies have found that a variety of signaling pathways are involved in the occurrence and development of renal fibrosis, and traditional Chinese medicine can intervene in the progression of renal fibrosis by regulating renal fibrosis-related signaling pathways. The purpose of this article is to review the mechanism of TCM intervention and regulation of renal fibrosis signaling pathway, so as to facilitate the study of the mechanism of action and active ingredients of TCM in the treatment of chronic kidney disease, further expand the scope of TCM treatment, and explore new ideas and methods for the treatment of CKD.***

Keywords: Renal fibrosis, Traditional Chinese medicine treatment, Signaling pathways, Research progress**.**

1. Introduction

Chronic Kidney Disease (CKD) refers to chronic structural or functional abnormalities in the kidneys caused by various factors (with a history of renal impairment exceeding three months). This condition includes the presence of renal injury markers (such as proteinuria, abnormal urine sediment, tubular abnormalities, histopathological abnormalities, or imaging findings) or a history of kidney transplantation, accompanied by or without a decline in glomerular filtration rate (GFR). It may also involve unexplained GFR reduction (below 60 mL/min) persisting for over three months. The primary pathological feature is renal fibrosis (RF) [1]. According to the survey, the prevalence of CKD is increasing year by year worldwide, and the prevalence of CKD in the general population has reached 14.3%. A cross-sectional epidemiological study in China shows that the prevalence of CKD in people over 18 years old is 10.8%. At the same time, about 1‰ of patients develop end-stage renal disease (ESRD) every year and need to receive renal replacement therapy [2]. Kidney fibrosis is a critical component in the progression of chronic kidney disease (CKD), involving abnormal activation of multiple signaling pathways such as AMPK/mTOR, TGF-β, NF-κB, and Wnt/β-catenin, which play pivotal roles in its development. While Western medicine has made significant progress in CKD treatment, challenges persist including kidney donor shortages, high treatment costs, and relatively high surgical risks. Meanwhile, growing research indicates that traditional Chinese medicine holds tremendous potential in preventing and managing renal fibrosis associated with chronic kidney disease.

In traditional Chinese medicine (TCM), renal fibrosis, though not classified under a specific disease name, falls within TCM categories such as “edema,” “guan ge” (kidney obstruction), “lun bi” (urinary retention), and “shen feng.” According to TCM diagnostic principles, its pathogenesis primarily involves blood stasis, internal heat-toxin accumulation, excessive dampness, and deficiency of vital energy. This article examines the effects of key signaling pathways associated with renal fibrosis, including AMPK/mTOR, TGF-β, NF-κB, and Wnt/β-catenin, while integrating TCM therapeutic approaches like blood-activating stasis-resolving therapy, heat-clearing detoxification, dampness-eliminating turbidity - reducing methods, and body-supporting pathogen - expelling techniques. Current research confirms that various herbal medicines and their active components can effectively alleviate renal fibrosis symptoms and slow the progression of chronic kidney disease by inhibiting overactivation of critical cytokines and signaling pathways, reducing oxidative stress and inflammatory responses, and regulating immune functions.

2. Study on Renal Fibrosis and Related Signaling Pathways

2.1 Pathological Changes in Renal Fibrosis

Kidney fibrosis is the deposition of fibrotic matrix and scarring in response to severe or sustained injury [3]. This persistent fibrosis eventually leads to loss of renal function. The histopathological changes in the renal fibrosis models of rats (large/small) are as follows: Han et al. [4] established a murine model of nephrotoxicity of cyclosporine by gavage with cyclosporine (30 mg/kg) combined with a low-salt diet. After modeling, the body weight of mice decreased, renal function decreased, glomerular basement membrane thickened, renal tubules dilated, vacuolar or atrophied. Zhang Jianwei et al. [5] established a mouse model of ischemia-reperfusion injury and renal fibrosis by ischemia-reperfusion surgery in vitro and in vivo. After modeling, ischemia-reperfusion injury caused pathological changes such as shedding of renal tubule epithelial cells, tubular structure disorder, disappearance of lumen structure and renal tubule dilation. Liang Guoqiang et al. [6] removed the left kidney and ureter, with a double ligation using 4-0 suture at the upper third of the ureter to establish a unilateral ureteral obstruction model in rats. Post-modeling, histopathological examination revealed glomerular enlargement, mesangial hyperplasia, tubular dilation, extensive inflammatory cell infiltration in the renal interstitium, along with glomerular and tubular interstitial

fibrosis. Extensive clinical practice and experimental data demonstrate that renal fibrosis is a primary factor leading to progressive loss of renal function. Therefore, in-depth investigation into the mechanisms of renal fibrosis holds significant importance for the prevention and treatment of renal failure.

2.2 Signaling Pathways Closely Related to Renal Fibrosis

Since radiofrequency (RF) exposure causes cellular dysfunction through multiple pathogenic factors including disrupted cytokines and signaling pathways, abnormal regulation of nuclear gene transcription may be one of the primary mechanisms underlying RF-induced renal fibrosis. Current research identifies key pathways such as AMPK/mTOR, TGF-β, NF-κB, and Wnt/β-catenin as being most closely associated with the development of renal fibrosis, though their detailed mechanisms remain under investigation.

2.2.1 AMPK/m TOR signaling pathway

The AMPK/mTOR signaling pathway plays a crucial role in regulating autophagy, which significantly impacts the progression of renal fibrosis. When AMPK is activated, it stimulates TSC1/2 protein activation, thereby inhibiting mTOR activity and inducing autophagy formation [7]. On one hand, autophagy in fibroblasts inhibits cell proliferation and promotes apoptosis, which helps improve renal fibrosis. On the other hand, the autophagic process plays a crucial role in regulating inflammatory responses in the kidneys. By enhancing autophagy, it reduces inflammatory levels in the kidneys and combats the progression of fibrosis. AMPK, as a positive regulator of autophagy, acts as an energy sensor that modulates cellular metabolism and homeostasis, thereby promoting autophagy. mTOR, a serine/threonine protein kinase serving as a negative regulator of autophagy, is responsible for cell growth, proliferation, motility, and survival, functioning as an inhibitor of autophagy [8]. Therefore, the AMPK/mTOR signaling pathway in renal fibrosis not only regulates cellular autophagy but also maintains cellular energy homeostasis. This pathway serves as a crucial survival mechanism during renal injury caused by fibrosis, profoundly influencing disease progression and treatment outcomes. Although AMPK is composed of α, β, and γ heterodimers, studies have shown that renal cells express AMPK in all its subtypes [9]. This suggests that in studies of renal fibrosis, there is no need to specifically distinguish between different AMPK subtypes, as they are universally present and active in renal cells. When cellular energy is depleted—such as during starvation or cellular stress—increased AMP/ATP ratios activate AMPK to maintain energy homeostasis [10]. This mechanism is particularly important in patients with renal fibrosis, who are already in a low-energy state. In this way, AMPK activation not only responds to the energy needs of the cell, but may also provide potential targets for the treatment of renal fibrosis.

2.2.2 TGF-β/ Smads signaling pathway

Transforming growth factor-β (TGF-β) plays a key role in kidney fibrosis, and it is now widely believed that TGF-β/Smad signaling is the main pathway to fibrosis, such as kidney fibrosis, liver fibrosis and pulmonary fibrosis [11]. TGF-β 1, as a key pro-fibrotic mediator, can regulate cell proliferation, differentiation, apoptosis, autophagy and ECM production, and plays an important role in kidney fibrosis together with downstream transcription factor Smad [12]. The role of Smad proteins in fibrosis regulation is complex, with competing pro-fibrotic and anti-fibrotic effects (including the regulation of mesenchymal transformation), and there are complex interactions between TGF-β/Smads and other signaling pathways [13]. Under pathological conditions, the expression of Smad2 and Smad3 is upregulated, while Smad7 is downregulated. However, blocking TGF-β through neutralizing antibodies, core proteoglycan proteins, or antisense oligonucleotides can prevent or improve fibrosis [14]. Therefore, the regulation of TGF-β signaling pathway is an important way to treat anti-nephrofibrosis.

2.2.3 NF-κB signaling pathway

The nuclear factor κ B (NF-κB) is a class of transcription factors that play a central regulatory role in renal fibrosis. They not only respond to harmful stimuli, but also rapidly activate in the early stages of renal fibrosis without new protein synthesis [15]. NF-κB, the primary cellular stress response system, consists of five key components: p65 (RELA), RELB, REL, NF-κB1 (p105/p50), and NF-κB2 (p/100/p52). These proteins are synthesized into preformed p105 and p100, which are then processed into p50 and p52 respectively. As transcriptional repressors lacking trans-activation domains, these factors play crucial regulatory roles in cellular responses [16]. The roles of these members in renal fibrosis are complex, involving the regulation of inflammatory responses, apoptosis, and fibrotic processes. NF-κB activation can occur through both classical and non-classical pathways. In the classical pathway, inflammatory cytokines such as TNF-α and IL-1β bind to their receptors, activating the NF-κB signaling cascade. This leads to the phosphorylation and degradation of IκB inhibitors, thereby releasing the p65/p50 complex which translocates into the nucleus to activate downstream gene expression. The non-classical pathway involves cytokine stimulation like CD40, causing p100 to be phosphorylated and processed into p52, forming the p52/RelB complex that further induces gene expression. Studies have shown that knockout of microfibril-associated protein 4 (MFAP4) inhibits the activation of NF-κB and TGF-β/Smad signaling pathways, while also downregulating the expression of fibrosis-related proteins [17]. This suggests that regulation of NF-κ B signaling pathway is an important way to treat anti-nephrofibrosis.

2.2.4 Wnt/β-catenin pathway

β-catenin cytoplasmic nuclear shuttle is considered to be an important feature of Wnt/β-catenin pathway activation [18]. In the process of kidney fibrosis, the activation of the Wnt/β-catenin signaling pathway is closely associated with its progression. When Wnt signaling is absent, β-catenin undergoes phosphorylation and degradation mediated by Axin in the cytoplasm, maintaining low levels of β-catenin in the cytoplasm. This suppression prevents transcription of nuclear target genes regulated by Wnt signaling [19]. When high levels of Wnt signaling are present in the extracellular environment, it induces the dissociation of the Axin/β-catenin

complex, thereby activating target gene transcription. Wnt proteins activate downstream factors to promote the transcriptional expression of target genes, leading to reduced β-catenin degradation and increased production of extracellular matrix components. This process facilitates the development of EMT and contributes to renal fibrosis [20]. Therefore, the role of Wnt/β-catenin signaling pathway in renal fibrosis can not be ignored. It directly participates in the development of renal fibrosis by regulating a series of target genes related to fibrosis.

3. Research on the Signaling Pathway of Traditional Chinese Medicine Intervention in Renal Fibrosis

In exploring Traditional Chinese Medicine (TCM) therapies for chronic kidney disease with renal fibrosis, we have identified multiple approaches that regulate distinct signaling pathways. These therapeutic strategies—blood-activating and stasis-resolving, heat-clearing and detoxification, dampness-eliminating and turbidity-resolving, as well as body-tonifying and pathogen-expelling methods—target specific pathological mechanisms of renal fibrosis. By modulating key biomolecules and signaling pathways, they achieve therapeutic effects through targeted interventions. This analysis will detail how these traditional approaches regulate critical biological pathways to address renal fibrosis.

3.1 Blood Activation and Blood Stasis Method

The term “blood stasis” was first proposed by Zhang Zhongjing in “Essential Prescriptions of the Golden Chamber”, where he pioneered the blood-activating and stasis-resolving therapy to treat various diseases, laying the foundation for subsequent generations in managing blood stasis disorders. Chronic illnesses can penetrate the meridians, with internal blood stagnation exacerbating conditions, thus requiring blood activation and stasis resolution. Hence the saying: “People know all diseases arise from qi, but few realize blood is the root cause of all ailments” (“Introduction to Medicine”). Numerous scholars also maintain that blood stasis persists throughout the progression of renal fibrosis.

Wang Munan et al. [21] found that leeches, represented by blood-activating herbs, and Sanqi (Panax notoginseng), known for resolving blood stasis, can enhance and maintain autophagy levels by inhibiting the PP2A/AMPK/mTOR signaling pathway. This dual mechanism not only suppresses renal fibroblast proliferation and improves renal interstitial fibrosis but also protects renal tubule cells and alleviates glomerulosclerosis. Zhu Weikun et al. [22] has demonstrated that Taohe Nengqi Decoction (a traditional Chinese medicine formula with blood-activating and stasis-resolving properties), which promotes bowel function and eliminates turbidity, can reduce serum creatinine (Scr) and blood urea nitrogen (BUN) levels in CRF rats. It improves renal tissue morphology, reduces inflammatory cell infiltration, and alleviates glomerulosclerosis and renal fibrosis. This effect may be achieved through two mechanisms: 1) blocking programmed cell death (PCD) by regulating the NLRP3/Caspase-1 pathway to delay renal fibrosis; 2) modulating the Wnt/β-catenin signaling pathway by inhibiting factors such as Wnt4, β-catenin, and MMP-7 to mitigate renal fibrosis. Wei Dandan et al. [23] demonstrates that the Blood-Activating and Stasis-Resolving Decoction (Xu Sha Zhu Yu Xia Er Shu Tang) effectively reduces renal fibrotic tissue and inflammatory cells in kidney fibrosis, alleviates tubular dilation or atrophy, and mitigates pathological changes. This therapeutic approach exerts its protective effect on renal tissue in rheumatoid fibrosing (RF) rats by downregulating TGF-β1, Wnt5a, and β-catenin protein levels while upregulating Smad7 and Wnt5b proteins. The study reveals that both single herbal components and compound formulations with blood-activating and stasis-resolving properties can significantly improve renal fibrosis treatment through targeted regulation of signaling pathways.

3.2 Heat-clearing and Detoxification Method

As renal fibrosis progresses over time, accumulated heat and toxins may develop. The “Su Wen: Zhi Zhen Yao Da Lun” (The Yellow Emperors Classic of Internal Medicine) proposes the therapeutic principle of “treating heat with cold,” advocating the use of heat-purging herbs to eliminate pathogens. Research demonstrates that heat-clearing formulas can address both “external toxins” like bacteria and viruses, as well as “internal toxins” such as oxygen free radicals and inflammatory cytokines, making them widely applicable in internal medicine, surgery, pediatrics, and miscellaneous diseases. The concept of “drowning toxin” was first documented in He Lianchens Qing Dynasty work “Revised Treatise on Extensive Warmth Theory”. It describes: “Drowning toxin... manifests as headaches with dizziness, blurred vision, tinnitus, hearing loss, nausea, vomiting, breath with a urine-like odor, occasional sudden epileptic episodes, and tongue coating with putrid patches and black spots.” These symptoms closely resemble those observed in chronic kidney failure and uremia stages according to Western medical standards.

Zheng Bowen et al. [24] has demonstrated that Compound Shelong Capsules (CSC), formulated with three herbal ingredients—Pseudostellaria heterophylla, Equisetum hirsute, and Hedyotis diffusa—can effectively alleviate renal fibrosis in ureteral ureteral obstruction (UUO) rats while protecting kidney function. The CSC mechanism may inhibit renal tubular epithelial-mesenchymal transition (EMT) progression through modulation of the Wnt4/β-catenin signaling pathway, thereby improving fibrosis and slowing disease progression. Additionally, Rendania glutinosa (RDP) enhances UUO-induced renal fibrosis through both classical and non-classical TGF-β signaling pathways [25]. By inhibiting NOD-like receptor heat protein domain 3 (NLRP3) inflammatory bodies and activating Toll-like receptor 4 (TLR4)/NF-κ B signaling, Huangkui Capsule alleviates renal tubular EMT in diabetic nephropathy and inhibits renal fibrosis [26]. Lee Kuan Yew et al. [27] found that BBR (Berberine, also known as Coptisine) treatment significantly inhibited the upregulation of NF-κ Bp65 protein signaling in kidney tissues of UUO mice. It reduced inflammatory cell infiltration, apoptosis, and collagen deposition in inflammatory foci, while decreasing the levels of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. Additionally, the expression of TGF-β 1 and its downstream molecule CTGF decreased in the kidneys of UUO mice, with marked reductions in matrix accumulation, α-SMA

expression, and apoptosis.

3.3 Dampness-eliminating and Turbidity-removing Method

The "Suwen: Great Treatise on Five Movements" states: "Its nature is tranquil and inclusive, its virtue is nourishing." Therefore, dampness and turbidity cause diseases that develop gradually rather than abruptly. They lie dormant internally, accumulating over time before manifesting. Initially appearing subtle and elusive, the symptoms are hard to discern and diagnose. The condition typically progresses slowly from mild to severe, with this concealment determining its persistent and delayed onset. This aligns with the characteristic of chronic kidney disease—its insidious onset and prolonged, difficult-to-treat progression. The "Lingshu: Chapter on Initial Manifestations of Diseases" further notes: "Dampness and turbidity injures the lower body," and "Clear dampness invades the deficient state, causing disease to originate in the lower body."

Jiang Qi and others [28] found that Uremic Kang, which removes dampness and turbidity, unblocks kidney meridians, and strengthens qi and spleen function, reduces p38 and ERK expression while inhibiting the MAPK pathway. Therefore, Uremic Kang can improve renal fibrosis caused by tubular epithelial-interstitial transformation by suppressing the p38/ERK MAPK pathway. — Cai Lin et al., 2023 [29] has demonstrated that flavonoids, the active components of rhubarb, exhibit anti-inflammatory, antibacterial, and antitumor properties. These compounds not only offer high cost-effectiveness and a long half-life, but also delay renal fibrosis in chronic kidney disease (CKD) rats by downregulating the p38MAPK signaling pathway. Additionally, corn silk extract regulates the NF-κB signaling pathway, inhibiting IKKβ, NF-κB activity, and IL-1β production in inflammatory mouse models, thereby mediating anti-inflammatory effects [30]. Based on unilateral ureteral obstruction, 5/6 nephrectomy animal model and TGF-β 1 induced renal fibroblast model, it was found that Poria acid A upregulates AMPK activity and inhibits TGF-β1/Smad3 pathway to inhibit fibroblast activation, abnormal synthesis of ECM, and reduce renal interstitial fibrosis [31]. The active ingredient quercetin in impatiens controls the mTOR and β-catenin signaling pathways, which reduces the activation of renal interstitial fibroblasts and renal interstitial fibrosis, while reducing the aggregation of macrophages and the expression of inflammatory factors TNF-α and MCP1 [32].

3.4 Support and Eliminate Evil

The classics state: Where deficiency exists, pathogenic factors will inevitably gather. The "Suwen: Comprehensive Commentary on Deficiency and Excess Disorders" further notes: "Excessive pathogenic factors lead to excess, while depletion of vital energy results in deficiency." In chronic kidney disease with renal fibrosis, the bodys struggle between pathogenic and righteous qi manifests both as pathogenic excess and righteous deficiency. During disease progression, when pathogenic forces overpower righteous qi, the condition worsens; when righteous qi prevails over pathogenic forces, recovery occurs. The "Suwen: Three Categories and Nine Subtypes Theory" advises: "Treat deficiency with tonification, excess with purgation." Treatment strategies should be tailored according to the severity and urgency of deficiency-excess states, such as adopting a "first attack then tonify," "first tonify then attack," or combined therapeutic approaches. Ultimately, the fundamental principle of supporting righteousness and expelling pathogens is to preserve righteous qi without leaving pathogenic remnants while eliminating pathogens without harming righteous qi.

Zhang Licaic et al. [33] has identified Professor Tang Shuifus empirical formula: the Detoxifying and Collateraling Formula (composed of Astragalus, Rheum palmatum, processed Pinellia ternata, Citrus aurantium, Smilax glabra, Bambusae rhizome, Atractylodes macrocephala, Eclipta prostrata, Sophora flavescens, Serpentine, Panax notoginseng, Eupolyphaga, and Seaweed), which may delay renal fibrosis in UUO rats by inhibiting the activation of the Wnt/β-catenin signaling pathway. Ma Jingjing et al. [34] indicated that the Kidney-Tonic and Profound-Opening Formula (comprising 11 Chinese medicinal ingredients: cicada slough, silkworm pupae, arctium seed, turmeric, kudzu root, rhubarb, snowdrop herb, astragalus, eucommia, cornus fruit, and danshen) may regulate the TGF-β1/Smad signaling pathway. This mechanism involves downregulating TGF-β and Smad3 protein expression while upregulating Smad7 protein expression, thereby participating in the progression of diabetic nephropathy. The formula demonstrates renal protective effects and inhibits the progression of renal fibrosis in diabetic nephropathy. Ma Xiuying et al. [35] found that liuwei Dihuang Tang, which is based on the principle of supporting and expelling evil, may inhibit inflammatory response by regulating NF-κ B, thus reducing renal fibrosis; it can also reduce fibrosis markers induced by TGF-β 1 and exert anti-fibrosis effect.

4. Conclusion

After an in-depth analysis of the pathological mechanisms of chronic kidney disease (CKD) and renal fibrosis, this paper reviews the research progress on the treatment methods of traditional Chinese medicine for renal fibrosis. Studies demonstrate that Traditional Chinese Medicine (TCM) effectively alleviates renal fibrosis symptoms by modulating key signaling pathways including AMPK/mTOR, TGF-β, NF-κB, and Wnt/β-catenin, while revealing potential molecular mechanisms underlying its therapeutic effects. These findings not only provide theoretical foundations for TCM applications in preventing and treating chronic kidney disease-related renal fibrosis, but also offer critical references for future research directions and therapeutic strategies. With ongoing clinical trials and basic research, TCMs comprehensive therapeutic efficacy in managing renal fibrosis is expected to be further validated. Furthermore, given the complexity and variability of renal fibrosis, deeper exploration of its intrinsic molecular mechanisms combined with modern molecular biology technologies is essential for achieving precision medicine. In conclusion, TCM as a therapeutic modality for renal fibrosis has shown significant potential. Future research should focus on its regulatory mechanisms and specific actions in the progression of renal fibrosis to optimize treatment outcomes.

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