

TGF- β Signaling: a Potential Therapeutic Target of Single Herbs and Extracts for Renal Fibrosis

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Abstract

Chronic kidney disease has emerged as a global public health problem in recent years. Chronic kidney disease progression, characterized by the development of renal fibrosis, leads to end-stage kidney disease. Transforming growth factor β has been shown to play a key role in the mechanism of renal fibrosis. Several studies have shown that individual Chinese herbal extracts can inhibit transforming growth factor β activation and reduce extracellular matrix formation, thereby imparting an anti-renal fibrosis effect through multiple pathways and multiple targets. In the present manuscript, the research trends of single traditional Chinese medicines and extracts in preventing and treating renal fibrosis are summarized, which may be insightful for generating new ideas for preventing and delaying renal fibrosis.

ΤΓΦ-β Σιγναλινγ: α Ποτεντιαλ Τηεραπευτις Ταργετ οφ Σινγλε Ηερβς ανδ Εξτρακτς φορ Ρεναλ Φιβροσις

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Abstract Chronic kidney disease has emerged as a global public health problem in recent years. Chronic kidney disease progression, characterized by the development of renal fibrosis, leads to end-stage kidney disease. Transforming growth factor β has been shown to play a key role in the mechanism of renal fibrosis. Several studies have shown that individual Chinese herbal extracts can inhibit transforming growth factor β activation and reduce extracellular matrix formation, thereby imparting an anti-renal fibrosis effect through multiple pathways and multiple targets. In the present manuscript, the research trends of single traditional Chinese medicines and extracts in preventing and treating renal fibrosis are summarized, which may be insightful for generating new ideas for preventing and delaying renal fibrosis.

Keywords Inflammation, Traditional Chinese Medicine, etiopathogenesis, transforming growth factor- β , kidney injury, fibrosis

Chronic kidney disease (CKD), a major health concern around the world, has been on the rise in recent decades. Over 26.9 million adults worldwide are suffering from CKD, which affects 497.5 million in the United States alone ¹. The pathogenesis of CKD is rather complex, involving mechanisms such as inflammation, oxidative stress, and proliferation and activation of cytokines and fibroblasts. Renal fibrosis is a prevalent and common pathological feature of CKD, with an incidence rate of 10.8% in China, and is rapidly becoming a major public health issue in many parts of the world²⁻⁴. Numerous studies suggest that transforming growth factor- β , TGF- β for short, stimulates TGF- β /Smad signaling pathway and promotes epithelial-mesenchymal transdifferentiation (EMT), which ultimately leads to renal fibrosis ⁵⁻⁷. While modern medicine involves the use of TGF- β antibody, gene therapy, hormone therapy, and angiotensin-converting enzyme inhibitors to treat a variety of fibrotic kidney diseases, the results are not satisfactory. Many studies ⁸⁻¹² have shown that the extracts of traditional chinese medicine can inhibit the activation of TGF- β and reduce the formation of extracellular matrix, thereby imparting an anti-fibrosis effect. Based on these findings, the present manuscript summarizes our knowledge of individual traditional chinese medicine and extracts targeting TGF- β to prevent or regulate renal fibrosis.

Rhubarb

Besides acting as an assistant drug, *rhubarb* helps cleanse the bowel, cool the blood, detoxify, dispel stasis, and dredge the meridians. *Rhubarb* is rich in *emodin*, which is a naturally occurring anthraquinone. *Rhein*, a substance in the anthraquinone group obtained from *rhubarb*, possesses anti-inflammatory, free radical-scavenging, and antifibrotic properties, which reduce kidney damage. Some researchers ¹³ believe that *rhein* can inhibit TGF- β 1 from inducing renal fibrosis and inhibit the expression and synthesis of fibronectin. A study ¹⁴ reported reduced expression level of TGF- β 1 in kidney tissue of rats in the rhein group compared to rats in drug groups. It was speculated that rhein could improve the pathological damage to kidney in diabetic obese rats by downregulating the levels of Smad3 and TGF- β 1. Researchers from China ¹⁵ found that *emodin* could reverse the transdifferentiation of renal tubular epithelial cells induced by TGF- β 1.

Astragalus membranaceus

Astragalus membranaceus invigorates the spleen and qi, assists detumescence, reduces dampness and moisture, acts as an antiperspirant, and prevents fever from developing. Among the major and active components of *A. membranaceus* is *astragaloside IV*, a small molecular saponin. Shan G et al.¹⁶ confirmed that *A. membranaceus* significantly inhibited alpha smooth muscle actin (α -SMA) expression increases and down-regulation of E-cadherin along with inhibition of Smad2/3 phosphorylation induced by TGF- β 1 in unilateral ureteral obstruction (UUO) mice model, thereby repressing Smad signaling pathway and alleviating renal fibrosis. A study ¹⁷ reported that *astragaloside IV* could reduce the expression of TGF- β 1 and Smad2/3 and inhibit tubulointerstitial fibrosis and tubular epithelial-mesenchymal transition. Another study ¹⁸ found that *astragaloside IV* could inhibit p38 mitogen-activated protein kinases (p38 MAPK), Jun amino-terminal kinases/stress-activated protein kinases (JNK/SAPK), and extracellular signal-regulated protein kinase 1/2 (ERK1/2) signaling pathways induced by TGF- β 1 in kidney tissue and regulate fibroblast differentiation and epithelial transdifferentiation.

Panax notoginseng

Sanqi, the root of *panax notoginseng* F. H. Chen, is one of the traditional chinese medicinal herbs widely used in china for stimulating blood circulation to disperse stasis, removing toxic substances, and subsiding swelling. *Saponin*, one of the main active ingredients in *P. notoginseng*, has been established to exert powerful anti-inflammatory, anti-toxic, and antifibrotic properties. Xu Y¹⁹ observed that *P. notoginseng* could downregulate TGF- β signal transduction pathway and alleviate renal interstitial fibrosis in rats with CKD. Xi et al. ²⁰ established a renal injury model by intravenous injection of cisplatin and speculated that *P. notoginseng* saponins might have played a role in reducing renal fibrosis by downregulating the expression of TGF- β 1, collagen-I (Col-I), and connective tissue growth factor in renal tissue. Li et al. ²¹ showed that

Sanqi injection could downregulate the levels of TGF- β 1 and p38 MAPK, indicating that it could protect the kidney by inhibiting the activation of TGF- β 1/p38 MAPK signaling pathway. Another study ²² has shown that *P. notoginseng saponin R1* could inhibit the expression of inflammatory cytokines, regulate extracellular matrix-related signaling pathways, and reduce the index of renal function damage in a diabetic nephropathy rat model, thus demonstrating its protective role in the kidney.

Salvia miltiorrhiza

In traditional Chinese medicine, *Salvia miltiorrhiza* is known for promoting blood circulation, relieving pain, and alleviating blood stasis. Among *S. miltiorrhiza*'s main ingredients are *aretanninone* and *salvianolic acid*. Ji et al. ²³ found that the immunohistochemical α -SMA and TGF- β are expressed in kidney tissue of UUO rats was significantly decreased in the *S. miltiorrhiza* injection group, which suggested that *S. miltiorrhiza* might directly inhibit the activation of TGF- β 1, a fibrotic pathway, and resist renal fibrosis. Some researchers ²⁴ believe that *salvianolic acid A* can regulate bone morphogenetic protein-7 (BMP-7)/Smad/TGF- β 1 signaling pathway, thereby blocking TGF- β 1 signal transduction into the nucleus. Another study ²⁵ found that in diabetic rats, *salvianolic acid* decreased the expression of TGF- β 1, p38 MAPK and Smad, suggesting that it might improve diabetic renal function and delay renal fibrosis by inhibiting TGF- β 1/p38 MAPK and TGF- β 1/Smad signaling pathways.

Curcuma longa

In Chinese medicine, *Curcuma longa* is believed to have the function of activating blood, moving qi, and relieving pain. The component of *C. longa* that has been extracted from the dried rhizomes is called curcumin. Zhu et al. ²⁶ found that curcumin inhibited the expression of TGF- β 1 and Col-I in epithelial cells, upregulated the expression of BMP-7, and reduced the transformation of human renal proximal tubular epithelial cell (HKC) into spindle cells induced by TGF- β 1. Ni et al. ²⁷ found that curcumin and demethoxycurcumin effectively improved renal fibrosis and speculated that its mechanism may be mediated by inhibition of the expression of fibronectin(FN), Col-I, and TGF- β 1.

Cordyceps

Besides tonifying and strengthening deficiency, *cordyceps* promotes blood circulation, removes blood stasis, maintains hemostasis, and removes phlegm. Yue et al. ²⁸ found that *C. mycelium* extract slowed down the progression of renal fibrosis by reducing the expression of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and renal fibrosis factors such as TGF- β 1 and matrix metalloproteinase 9 (MMP-9). Chen et al. ²⁹ showed that *Cordyceps* preparation alleviated renal fibrosis, and the possible underlying mechanism was that it could inhibit the EMT by downregulating TGF- β /Snail signaling pathway in renal tubular epithelial cells of diabetic mice.

Rhodiola rosea

Rhodiola rosea is used to stimulate qi, stimulate the spleen, and dredge collaterals. A major component of *R. rosea* is salidroside, which is known to suppress inflammation and possess immunostimulating, antioxidant, and antitumor activities. Liu ³⁰ confirmed that salidroside could delay the progress of renal fibrosis, and its underlying mechanism may be the inhibition of the expression and synthesis of Col-I and Col-III induced by TGF- β 1 in HK cells, which reduces the rate of degradation. Leng et al. ³¹ found that salidroside upregulated the expression of E-cadherin, while reducing that of N-cadherin and alpha-smooth muscle actin (α -SMA), thus alleviating the oxidative stress in rats.

Notopterygium

Notopterygium can dispel wind, eliminate dampness, dredge meridians, reduce swelling, and provide pain relief. According to traditional Chinese medicine, one of the main chemical components of *Notopterygium* is nodakenin, which is known to depress qi, reduce phlegm, dispel wind, and clear heat. Huang et al. ³² reported that nodakenin could suppress the expression of Smad2/3 signaling proteins downstream of TGF- β 1, reduce the expression of signaling pathway-related proteins, and delay the progression of renal interstitial fibrosis.

Tripterygium wilfordii

Tripterygium wilfordii is known to clear dampness, promote detoxification, promote blood circulation, and reduce inflammation. *Polyglycoside* and *tripterine* are among the main monomer components that can be derived from *T. wilfordii*. Yang³³ found that polyglycoside from *T. wilfordii* inhibited cell proliferation in vitro and alleviated glomerular fibrosis by inhibiting TGF- β activation and nuclear factor (NF- κ B) inflammatory reaction. Some researchers³⁴ have reported that triptolide can reduce the expression of TGF- β 1 and Smad3 in kidney tissue and upregulate the expression of Ski protein, thereby alleviating renal fibrosis.

Cnidium monnieri

Cnidium monnieri is believed to promote health by warming the kidney, activating "yang," expelling wind, and eliminating dampness. The main active ingredient of *C. monnieri* is epothilone, which has antispasmodic, antihypertensive, immunity strengthening, and anti-inflammatory properties. Zhang et al.³⁵ reported that *epothilone* significantly inhibited the activation and proliferation of renal fibroblasts both in vivo and in vitro, and selectively inhibited TGF- β 1/ Smad signaling pathway during the activation of renal fibroblasts, thus imparting an anti-fibrosis effect.

Paeonia lactiflora

Paeonia lactiflora, a type of a paeony, is effective in calming the liver, relieving pain, nourishing blood for regulating menstruation, astringing Yin, and curing hydroschesis. The main constituents of *P. lactiflora* are glucosides, which have demonstrated anti-inflammatory, analgesic, antispasmodic, liver-protectant, and immunoregulating properties in previous studies³⁶⁻⁴⁰. Lin et al.⁴¹ reported that total glycosides of *P. lactiflora* downregulated NF- κ B and toll-like receptor 4 (TLR4) expression in the kidneys of rats, inhibited the synthesis of TGF- β 1, reduced the deposition of extracellular matrix, and delayed the progression of renal fibrosis.

Safflower

The blood-stimulating effects of *safflower* include eliminating blood stasis, relieving pain, stimulating blood circulation, and opening meridians. In previous studies, *safflower* yellow, a flavonoid, was found to be the main active component of safflower, which is widely used in traditional Chinese medicine owing to its anti-inflammatory and antioxidant effects. Dong et al.⁴² reported that the treatment with *safflower* led to downregulation of the expression of NF- κ B, TGF- β 1, reduced the effect of urinary tubular protein, improved the pathological changes in the kidneys of UUO rats, protected renal tubular function, and delayed the occurrence of renal fibrosis.

Erigeron breviscapus

Erigeron breviscapus is believed to dispel pathogenic wind and dampness, aid blood circulation, free the meridians, and lead to detumescence, thereby relieving pain. *Breviscapine* is a natural drug derived from the flavonoids of *E. breviscapus*. Xu et al.⁴³ reported that *breviscapine* reduced the expression levels of TGF- β 1 and plasminogen activator inhibitor-1 (PAI-1) mRNA in kidney tissue, and also reduced the expression levels of inflammation-related factors as IL-1 β and TNF- α . It is suggested that *breviscapine* can alleviate renal interstitial fibrosis in UUO rats, and its underlying mechanism involving downregulation of the expression of TGF- β 1 and α -SMA may impart an anti-fibrosis effect.

Pueraria lobata

Pueraria lobata, one of the most popular traditional Chinese medicines, is believed to remove wind and relieve pain from the outside. *Puerarin* is a major component isolated from the roots of *P. lobata*. Wang et al.⁴⁴ have reported that *puerarin* regulated the expression of MMP-1, MMP-3, and MMP-10, reduced the levels of TNF- α and TGF- β 1, decreased the expression of FN in renal tissue, inhibited the expression of connective tissue growth factor (CTGF) mRNA and its protein in diabetic rats, and reduced the deposition of extracellular matrix, thereby delaying the progression of renal fibrosis.

Ginseng

Herbal medicines such as ginseng that can tonify qi and nourish Yin are highly effective in traditional Chinese medicine. *Ginsenoside*, one of the effective components in *ginseng*, harbors a variety of biomedical properties such as anti-aging, anti-diabetic, anti-cancer, and immunomodulating effects. Zhang et al.⁴⁵ have reported that *ginsenoside Rh1* alleviated renal fibrosis in UUO rats by regulating TGF- β 1 related signal transduction pathway and inhibiting the expression of type I collagen and its downstream activators CTGF and α -SMA.

Schisandra

The traditional Chinese medicine *Schisandra*, with many biological activities, is known to exhibit strong anti-inflammatory and antioxidant properties. *Schisandrin B*, an active ingredient in lignans derived from *Schisandra*, is a traditional Chinese herbal medicine. *Schisandrin B* harbors various biological properties such as antioxidant, anti-bacterial, anti-inflammatory, and anti-tumor properties. Zheng et al.⁴⁶ observed that *schisandrin B* significantly reduced renal interstitial fibrosis as evident from increased expression of E-cadherin and decreased expression of TGF- β 1, α -SMA, Col-I, and p-Smad3. This suggests that *schisandrin B* can alleviate renal fibrosis by inhibiting TGF- β /Smad3 signaling pathway.

Hedyotis diffusa

The traditional Chinese herb *Hedyotis diffusa*, also known as Bai Hua She Cao, belongs to family Rubiaceae. It is widely distributed in South China and other Asian countries. Based on the theories of Chinese medicine, *H. diffusa* has significant effects on dispersing wind, relieving pain, promoting blood circulation, detoxification, and reducing swelling. Several lines of evidence have demonstrated that *H. diffusa* exhibits anti-inflammatory, immune-regulating, and antioxidant properties. A Chinese research group⁴⁷ studied the effect of iridoid compounds of *H. diffusa* on renal fibrosis and elucidated its underlying molecular mechanism. They analyzed and screened 20 signaling pathways including TGF- β and JAK-STAT signaling pathways and found that the compound-target network contains 10 compounds and 111 related targets.

Cynanchum auriculatum

In traditional Chinese medicine, the herb *cynanchum auriculatum*, also called as "Baishouwu", is one of the most famous tonics. It is known to provide nutrients to the liver and kidneys, regulate blood and dryness, protect the liver, and show antitumor effects. According to various reports⁴⁸⁻⁵⁰, the main components in *C. auriculatum* are steroids. Some researcher⁵¹⁻⁵³ found that C-21 steroidal glycoside of *C. auriculatum* inhibited phosphorylation of MAPK family proteins such as ERK1/2 and Smads family proteins such as Smad2 and Smad3 in the liver and kidney tissues and reduced the mRNA expression levels of inflammatory factors such as interleukin-6 (IL-6) and TNF- α . Additionally, it suppressed the upregulated levels of fibrosis-related proteins Col-I and Col-III.

Scutellaria baicalensis

Scutellaria baicalensis is a species of flowering plant in the Lamiaceae family that is traditionally used to cool heat, drain fire, clear damp heat, stop bleeding, calm the fetus, and descend yang. *S. baicalensis* harbors flavone compounds such as baicalin and its glucuronide and baicalein. Zheng et al.⁵⁴ have reported that baicalin inhibited EMT and significantly improved renal fibrosis. It reduced the FN and Col-I mRNA expression levels, downregulated α -SMA level, and increased the expression level of E-cadherin by inhibiting TGF- β 1 production and its downstream signal transduction. Tan et al.⁵⁵ have elucidated the effects of baicalin at different times and different doses on renal fibrosis in UUO rats, and speculated that baicalin could inhibit the process of renal fibrosis in UUO rats by inhibiting Notch1/Jagged1 pathway, a non-Smads signaling pathway, which is induced by TGF- β 1.

Poria cocos

Poria cocos, recorded in the Chinese pharmacopoeia as an herb, possesses diuretic, detumescent, and detoxifying properties. Previous reports⁵⁶⁻⁵⁹ have suggested that *triterpenes*, *polysaccharides*, and *steroids* are

the main chemical components of *poria cocos*. The mechanism of diterpenes *poricoic acid ZF* and triterpenes (*poricoic acid ZG* and *poricoic acid ZH*) extracted from *poria cocos* is to block the interaction among Smad anchor for receptor activation (SARA), TGF- β 1, and Smad3 and selectively inhibit the phosphorylation of Smad3. Based on the above findings, Cai Y et al.⁶⁰ studied renal fibrosis in UUO mouse model, which was mediated by angiotensin II and TGF- β 1, and revealed that 3,4- ring-opening lanosterone triterpene acids *poricoic acid ZC*, *poricoic acid ZD*, and *poricoic acid ZG* and lanosterone triterpene acids *poricoic acid ZE* and *poricoic acid ZH* play an anti-renal fibrosis role by selectively inhibiting the phosphorylation of Smad3 and inhibiting RAS and Wnt/ β -catenin signaling pathways.

Rhizoma alismatis

Rhizoma alismatis is used to clear dampness and heat and to facilitate diuresis in Chinese medicine system. The main active components of *R. alismatis* are triterpenoids, an important group of triterpenes. Chen et al.⁶¹ have reported that triterpenes have anti-renal fibrosis effect, a presumed underlying mechanism for which may be by inhibiting the classic Wnt/ β -catenin signaling pathway and regulating the p-Smad3 and Smad7 expression. TGF- β 1 can inhibit β -catenin and the downstream targets such as PAI-1, MMP-7 and ferroptosis suppressor protein 1 in NRK-52E cells.

Stephania tetrandra

The Chinese medicinal herb *Stephania tetrandra* contains the strong compound *tetrandrine* as one of its main active ingredients. The herb is believed to be instrumental in getting rid of wind, cold, and dampness and in clearing away heat and fire. Bai et al.⁶² have reported that *tetrandrine* combined with hormone group reduced the positive expression of CTGF and upregulated the expression of MMP-13, which are dose-dependently associated with the risk of renal fibrosis. The results showed that *tetrandrine* could enhance the expression of MMP-13, promote the degradation of extracellular matrix, and inhibit the proliferation of extracellular matrix by inhibiting the expression of CTGF. As a downstream effector of TGF- β 1, CTGF has been demonstrated to cause renal tissue injury and renal fibrosis.

Outlook

The pathophysiological hallmark of CKD is fibrosis. Nearly all CKDs are characterized by fibrosis, and consequently, renal fibrosis is one of the therapeutic targets for the treatment of CKD. Inevitably, once renal damage occurs, renal disease progresses, leading to the hypothesis that there are common underlying pathogenic pathways leading to end-stage renal disease (ESRD). Additionally, pathological processes such as fibrosis and inflammation are enhanced in CKDs. TGF- β 1 is considered a key mediator of fibrotic signaling in renal epithelial cells, and is responsible for causing renal fibrosis as a final manifestation of CKD. The use of Chinese medicinal plants and extracts aimed at preventing renal fibrosis has burgeoned in the last few decades. Traditional Chinese medicines can act on a variety of molecular pathways to delay renal fibrosis. However, many cytokines are involved in the pathogenesis of renal fibrosis, and many signaling pathways are involved, thus rendering the process complicated and tedious. There is consensus on the importance of elucidating the interactions among these pathways and understanding the whole network with a particular focus on the intersection of these pathways, to find the best treatment plan. At present, many experimental studies on anti-renal fibrosis effects of traditional Chinese medicines are ongoing at in vitro and translational levels, but the in-depth knowledge and systematic research is still lacking. Based on the theory of traditional Chinese medicine, detailed studies on individual traditional Chinese medicines and their effective components along with modern medicine are warranted to systematically explore the underlying mechanisms of traditional Chinese medicines in preventing and treating renal fibrosis, and with the aim to develop new drugs with few side effects.

Declarations

Running Title

TGF- β Signaling

Ethics approval and consent to participate

This study will not involve the individual patient and any ethical problems since its outcomes are based on published data.

Consent for publication

Authors are responsible for correctness of the statements provided in the manuscript.

Availability of data and materials

This is a review about TGF- β signaling as a potential therapeutic target of single herbs and extracts for renal fibrosis. All data and materials are from published papers.

Competing interests

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Gengzhen Huang, Yaodan Zhang and Yuerong Ma conceived the idea. Yingying Zhang analyzed data and literature. Gengzhen Huang, Chao Hu and Yaodan Zhang wrote the manuscript.

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