

Chinese herbal formulas and renal fibrosis: An overview

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Abstract: All forms of chronic kidney disease (CKD) eventually lead to renal fibrosis irrespective of its origin. It is generally characterized by an excessive accumulation and deposition of extracellular matrix (ECM) and to date no ideal treatment has been established. Bian-Zheng-Lun-Zhi (syndrome differentiation and treatment), a classic feature of traditional Chinese Medicine (TCM), is a unique method used to diagnose and treat the pathology of a disease. Zheng (syndrome) is used to demonstrate the nature of a disease completely in an extensive and specific manner. Chinese herbal formulas are determined according to TCM theory and this review highlights these formulas and suggests possible mechanism for their use in the treatment of renal fibrosis.

Keywords: Chinese herbal formula; Bian-Zheng-Lun-Zhi; renal fibrosis; chronic kidney disease

1. INTRODUCTION

Chronic kidney disease (CKD) prevalence is estimated to be 8-16% and is becoming a major public health concern.. Moreover, it is ranked the third highest for years of life lost due to premature mortality (82%), behind AIDS and diabetes mellitus [1-3]. Renal fibrosis is the final, common pathological feature of every progressive CKD regardless of etiology [4]. The molecular mechanisms of renal fibrosis are associated with inflammatory cell infiltration, myofibroblast proliferation and epithelial-mesenchymal transition (EMT), as well as extracellular matrix (ECM) overproduction [5, 6]. However, these complex mechanisms responsible for renal fibrosis are still poorly understood. The existing therapies are not ideal for the treatment of CKD and hence there is an urgent need to explore the pathophysiological mechanisms underlying renal fibrosis and to discover safe and new strategies for its treatment.

Recently, Traditional Chinese Medicine (TCM) has been increasingly used in the treatment of renal disorders due to its clinical efficacy and safety [7]. Bian-Zheng-Lun-Zhi (syndrome differentiation and treatment) is one of the most fundamental characteristics of TCM, which is a unique method to diagnose and treat the pathology of a disease. The Bian-Zheng entails analyzing, inducing, judging and summarizing the clinical data of symptoms and signs by four

diagnostic methods (inspection, listening and smelling, inquiry, taking pulse and palpation) to identify a certain Zheng (namely syndrome, a comprehensive description of the pathological process of a disease at a particular stage) [8-11]. This therapeutic principle is suggested according to the results of syndrome differentiation and the process is named Lun-Zhi, which is the standard methodology used in clinical treatment by TCM practitioners [9].

In the viewpoint of TCM, renal fibrosis is a pathological process due to a long-term imbalance between healthy qi and pathogenic factors leading to deficiency of healthy qi. Therefore, spleen-kidney deficiency (kidney-yin or yang deficiency) is an internal condition and a key factor in the development of renal fibrosis. This provides the main principle on which the treatment of renal fibrosis is based. Chinese herbal formulas are determined on the basis of TCM theory, which provides multiple functions with several medicines, and appropriate herbs can be prescribed with flexibility to suit the specific syndrome.

Due to different factors and mechanisms involved in the pathogenesis of renal fibrosis, Chinese herbal formulas which display multi-channel and multi-target properties are being applied to clinical practice to treat renal fibrosis. Therefore, this review mainly focuses on the formulas which have been commonly used in patients and display potential antifibrosis properties. Peer-reviewed articles were gathered by consulting the databases PubMed, Elsevier, Springer and Scholar and the search terms included renal, kidney, fibrosis, traditional Chinese medicine and formula.

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2. THE PATHOPHYSIOLOGICAL MECHANISM OF RENAL FIBROSIS

The histological characteristics of renal fibrosis include tubular atrophy and dilatation, interstitial leukocyte infiltration, increased fibroblasts and accumulation of collagen and ECM [12-14]. Therefore, an array of intra- and extracellular mechanism is critical in the prevention of renal fibrosis. With the help of molecular and cell biology technology and renal fibrosis animal models, it is generally accepted that the pathophysiology of renal fibrosis has been depicted as four overlapping phases namely: priming, activation, execution and progression [15, 16].

The first phase is cellular activation and injury stage, ongoing inflammatory stimulation triggers the activation of tubular epithelial cells and infiltration of inflammatory cells, including lymphocytes, monocytes/macrophages, dendritic cells and mast cells [17, 18]. The second phase is the fibrogenic signaling phase when several profibrotic cytokines are released accompanying the activation of matrix-producing cells. Recent studies have focussed on myofibroblasts, a subpopulation of activated fibroblasts, which are derived from bone-marrow, renal interstitial fibroblasts, vascular pericytes, endothelial and tubular cells, which contribute to the massive proliferation and excessive ECM accumulation [15, 19-21]. During the third phase, the excessive deposition of ECM, such as collagen I, III and fibronectin, leads to the development of renal fibrosis [22, 23]. In the last phase, the renal structure and function gradually disappear with sustaining ECM accumulation, which results in the majority of the undesirable consequences of fibrosis.

Renal fibrosis is an enormously complex, dynamic process that involves almost all types of renal cells and the infiltrated cells. Nevertheless the mechanisms implicated in renal fibrosis are still not entirely clear which raises the question of how to control renal fibrosis.

3. CHINESE HERBAL FORMULAS FOR TREATING RENAL FIBROSIS

Many beneficial medicinal formulas, including patent medicines, classic prescriptions and empirical recipes, are extensively documented in the TCM systems in many cultures. Among these, there are plenty of Chinese herbal formulas with anti-fibrotic effects which have been used for the treatment and prevention of renal fibrosis. Here are some typical examples, and others are presented in Table 1.

Niaoduoqing granule (NDQG), also known as Uremic Clearance granules, includes: *radix et rhizoma rhei*, *radix astragali*, *radix glycyrrhizae*, *rhizoma atractylodis macrocephalae*, *radix polygoni multiflori preparata*, *Flos chrysanthemi*, *radix salviae miltiorrhizae*, *radix codonopsis*, *radix bupleuri*, *cortex mori*, *radix sophorae flavescentis*, *radix paeoniae alba*, *herba plantaginis*, *rhizoma pinelliae*, *poria* and *rhizoma ligustici*. This is the first TCM approved by the State Food and Drug Administration (SFDA, China) for the treatment of CKD as a Chinese patent medicine, and has been widely used in clinical practice for the lowering of serum creatinine (Scr), blood urea nitrogen (BUN) and renal protection [24-26]. NDQG therapeutical effects are due to the

promotion of ECM degradation, regulation of MMP-2/TIMP-1 balance and the inhibition of TGF- β 1/smad signal pathway in an unilateral ureteral obstruction (UUO) model. NDQG also can prevent EMT and suppress vimentin and α -SMA expression, as well as restore E-cadherin expression thus confirming that NDQG may be a promising agent of anti-fibrosis [27, 28].

Huangqi decoction (HQD), which comprises of *Astragalus*, *Poria*, *Trichosanthes*, *Ophiopogon*, *Schisandra*, *Licorice* and *Rehmannia*, is originally recorded in Yang shiying's Renzhai Zhizhi Fanglun at Northern Song Dynasty. It is one of the most classic recipes in the clinical treatment of CKD and according to the TCM theory, HQD can tonify kidney-qi [29, 30]. Recently, significant progress has been made in the molecular mechanisms responsible for the treatment of CKD by HQD. It was reported that HQD can reverse structural and functional alterations in 5/6 nephrectomized rats by inhibiting NADPH oxidase expression, ROS production and promoting NO production [31]. In addition, HQD ameliorates renal fibrosis in an (UUO) model through not only inhibiting transforming growth factor- β 1 (TGF- β 1)/Smad signal pathway, but also by activating Wnt/ β -catenin signal pathway [29, 32].

Kangxianling granule (KXLG), which is composed of *Radix salviae miltiorrhizae*, *prepared rhubarb*, *angelica*, *Achyranthes* and *peach kernel*, is an empirical formula which was developed to treat CKD as well as early and mid-stage renal fibrosis by Shuguang Hospital of Shanghai University of TCM [33-35]. Based on previous studies, KXLG prevents renal fibrosis probably by inhibiting TGF- β , Smads, angiotensin II, tumor necrosis factor- α (TNF- α), nuclear factor- κ B (NF- κ B), and eventually leads to a series of changes that: 1) inhibit tubular epithelial cell apoptosis; 2) inhibit myofibroblasts trans-differentiation; 3) inhibit the proliferation of inflammatory cells and 4) reduce the EMT transition [36, 37].

4. SUGGESTED MECHANISMS

From the perspective of TCM, renal fibrosis is a leading cause of kidney-qi deficiency syndrome [38]. Therefore, tonifying kidney-qi, including invigorating kidney-yang and nourishing kidney-yin, is the main consideration in clinical practice. Yougui pill, a yang-tonic prescription, is used for the empirical treatment of renal fibrosis [39] and Fuzheng huayu formula is a SFDA approved anti-fibrotic medicine in China, which can not only activate blood and remove stasis, but also nourish yin [40].

At present, extensive studies have been carried out to explore the molecular mechanisms of Chinese herbal formula in the treatment of renal fibrosis. The development and progression of renal fibrosis is primarily involved in the trans-differentiation of kidney inherent cells such as mesangial, epithelial or endothelial cells or fibroblasts into myofibroblasts, and infiltration of inflammatory cells, regulated by numerous growth factors and cytokines, eventually leading to ECM excessive deposition [41, 42]. Emerging evidence indicates that about 30% of myofibroblasts are generated via EMT (epithelial-mesenchymal transition) pathway in diseased kidney [43].

Hence epithelial cells lose intercellular adhesion molecules E-cadherin and synthesize α -smooth muscle actin (α -SMA) as well as actin reconstruction, which plays a crucial role in renal fibrosis [44-46]. Qizhuxiezhao Fang protects kidney against fibrosis through inhibiting EMT transition via upregulating E-cadherin and downregulating α -SMA [47].

It is reported that EMT can be initiated by transforming growth factor- β 1 (TGF- β 1) [48] a well known cytokine, which is regarded as a central mediator of renal fibrosis [49]. There is considerable evidence which suggests that TGF- β 1 is substantially increased in the injured kidney in both animal disease models and CKD patients [50, 51]. TGF- β 1 not only induces proliferation, migration of different types of renal cells, but also regulates various ECM proteins synthesis and degradation [52, 53].

In addition to these, previous studies have suggested that TGF- β 1 can decrease the activation of MMPs, induce the expression of connective tissue growth factor (CTGF) and platelet derived growth factor-B (PDGF-B) [54-56]. MMPs are a large family of zinc-dependent endopeptidases that play a central role in the degradation of ECM, while the activity of MMPs can be down regulated by tissue inhibitors of metalloproteinases (TIMPs) [57]. Among these, gelatinases (MMP-2, -9) predominantly degrade collagen, a major component of ECM [58, 59]. CTGF has been shown to promote myfibroblast activation and ECM accumulation [60] whilst PDGF is known to stimulate glomerular mesangial cell proliferation and ECM deposition [61, 62].

The current evidence shows that TGF- β 1/Smads signal pathway is the most classic signaling pathway in the progression of renal fibrosis [63]. Consistent results from numerous studies indicate that TGF- β 1/Smads signal pathway can be inhibited by decreasing Smad2/3 and increasing Smad7 and these may have antifibrosis effects [64, 65]. Above of all, targeting the TGF- β 1 downstream effectors or the signaling that mediates its fibrogenic action will become a new therapy in the treatment of renal fibrosis, and several Chinese herbal formulas are being developed for this purpose such as Shenqi Wan and Tongxin Luo [66, 67].

Current research shows that renal fibrosis also can be considered as an inflammatory process which is associated with the increased expression of tumor necrosis factor- α (TNF- α) and with the activation of NF- κ B [68, 69]. TNF- α participates in the infiltration and activation of inflammatory cells and in the transformation of epithelial cells and fibroblasts into myofibroblasts [52]. Decreased NF- κ B levels has been reported to attenuate renal injury and inflammation in different animal models of CKD [70, 71]. Therefore, anti-inflammation agents are attractive therapeutic target for attenuating the inflammatory process, such as Fuzheng Huayu Formula [40].

Oxidative stress in progressive renal disease has been highlighted by emerging data in which antioxidant therapeutics target mitochondrial reactive oxygen species (ROS) and especially ameliorate renal fibrosis lesions in the experimental models [72]. Recent studies indicate that TGF- β 1 stimulates the generation of ROS by activating nicotinamide adenine dinucleotide phosphate (NADPH)

oxidase that activates p38 mitogen-activated protein kinases (MAPK), Jun N-terminal kinase (JNK), extracellular-signal-regulated kinase (ERK) signaling [73]. Some Chinese herbal formulas could prevent renal fibrosis via antioxidative stress, such as Wenpitang Hab Wuling san [74].

From what has been discussed above, the underlying mechanisms of Chinese herbal formulas to prevent renal fibrosis could inhibit renal cell proliferation, inflammatory cell infiltration and reduce oxidative stress via stimulating or suppressing growth factors, cytokines, proteins, as well as modulating signaling pathways. However, more evidence is needed to confirm or investigate new mechanisms for treating renal fibrosis. The common pathway involved in the treatment of renal fibrosis is shown in Fig.1.

5. CONCLUSIONS AND PERSPECTIVES

CKD is an increasingly common condition with limited treatment options that is placing a major financial and emotional burden on the community. Renal fibrosis is also most relevant with the rate of progression of renal dysfunction [75]. The pathogenesis of renal fibrosis can be artificially divided into four phases. However, such a division is arbitrary, as in reality renal fibrogenesis is a dynamic process in which many of these events occur concomitantly [16], hence, using a single-target strategy for the renal fibrosis treatment is not reliable. At present, more attention has been focused on TCM with its well defined and established therapeutic system. Bian zheng lun zhi, the classic theory of TCM, provides a multi-link and muti-path comprehensive method for preventing and treating renal fibrosis. Chinese herbal formulas combine different herbal compounds to increase or promote therapeutic effectiveness, minimize toxicity and side effects, and optimize the therapeutic effects of each component, which can provide a safe and effective therapy in the treatment of renal fibrosis.

Currently, limited experimental studies involving the level of cytology and protein expression have been conducted on Chinese herbal formulas. This article has presented and analyzed the Chinese herbal formulas effective against renal fibrosis and their suggested mechanisms have been outlined Chinese herbal formulas can act as anti-fibrosis agents due to their anti-proliferative, anti-inflammatory and anti-oxidant properties and have been applied clinically. However, it is still necessary to search for novel formulas for treating renal fibrosis. Although several distinct targets and common molecular signal pathways have been disclosed, the details of the anti-fibrosis mechanisms of the Chinese herbal formulas involved need to be clarified further. Furthermore, the active substances of the Chinese herbal formulas, their synergy with a variety of prescription drugs and interactions with new pharmaceuticals need to be investigated further.

In summary, the focus of future clinical research should be to combine TCM theory with the latest medical research and in order to explore more effective and less toxic formulas, investigate their underlying mechanisms, and develop effective new dosage forms.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1 The Chinese herbal formulas from medicinal plants displaying anti-fibrosis properties

Formula	Constitute	Model / Cell type	Mechanism	Ref
Shenqi Detoxification Granule	Radix Astragali, Salvia miltiorrhiza, Angelica sinensis, Rheum officinale, Gordon Euryale seed, Herba Ecliptate, radix semiaquilegiae, rhizoma imperatae, Prepared aconite lateral root, herb of Shorthorned Epimedium, Cherokee Rose Fruit, Hedyotis diffusa.	Adenine-induced CRF model UUO	Inhibit PDGF-B, CTGF expression and ET/NO. Inhibit TGF- β 1-mediated EMT and TGF- β 1-Smad-ILK signal pathway	[76, 77]
Shenqi wan	Radix Rehmanniae, Cortex Moutan, Dogwood, Poria cocos, Yam, Alisma, Cassia Presl, Monkshood.	Adenine induced model	Inhibit TGF- β 1/Smad signal pathway	[66]
Tongxinluo	Panax ginseng, Ziziphus jujube Mill. var. spinosa, Paeonia lactiflora Pall, Santalum album, Dalbergia odorifera, Boswellia carteri Birdw, Borneolum syntheticum, Scolopendra subspinipes mutilans, Buthus martensii Karsch, Steleophaga plancyi, Hirudo nipponica, Cryptotympana pustulata Fabricius	High-fat induced DN model GECs and GMCs	Inhibit the transfer of TGF- β 1 from GECs to GMCs through exosomes	[67]
Fuzheng Huayu Formula	Salvia miltiorrhiza, Pollen Pini, Fermentation Mycelium Powder, Semen Persicae, Fructus Schisandrae Chinensis, Gynostemma Pentaphyllummak	HgCl ₂ induced RIF model	Decrease α -SMA, TNF- α , NF- κ B, MMP-2, p-I κ B	[40]
Quwan Chencuo Formula	Salvia miltiorrhiza, Radix et Rhizoma Rhei, Cortex Moutan, Semen Persicae, Radix Puerariae, Poria cocos (Schw.) Wolf, Semen Plantginis Asi-aticeae, Arecae Pericarpium, Rehmannia glutinosa (Gaertn.) Li-bosch, Cornus officinalis Sieb. Et Zucc	UUO	Decrease TGF- β 1, α -SMA and increase E-cadherin expression,	[78]
Dahuang Fuzi Decoction	Radix et Rhizoma Rhei, Radix Aconiti Lateralis Preparata, Radix et Rhizoma Asari	Aristolochic acid nephropathy model	Decrease collagenI, III, increase MMP	[79]

CRF: chronic renal failure; CTGF: connective tissue growth factor; DN: diabetic nephropathy; EMT: epithelial-mesenchymal transition; ET/NO: endothelin / nitric oxide; GECs: glomerular endothelial cells; GMCs: glomerular messangial cells; ILK: integrin linked kinase; MMP: mitochondrial membrane potential; NF- κ B: nuclear factor-Kappa B; PDGF-B: platelet-derived growth factor-B; p-I κ B: phosphor-inhibitor-Kappa B; RIF: renal interstitial fibrosis; TGF- β 1: transforming growth factor- β 1; TNF- α : tumor necrosis factor- α ; UUO: unilateral ureteral obstruction; α -SMA: α -smooth muscle actin.

Formula	Constitute	Model / Cell type	Mechanism	Ref
Qingxuan Jiangya Decoction	Caulis Bambusae in Taeniam, Poria cocos, Gentiana scabra, Ligusticum chuanxiong Hort, Gastrodia elata, Scutellaria baicalensis, Coptis chinensis, Acorus calamus, Os Draconis, Ostrea gigas, Gardenia jasminoides, Taxillus sutchuenensis, Prunella vulgaris	Spontaneously hypertensive rat model	Inhibit TGF- β 1/Smad signal pathway, decrease collagenI, III, MMP-2,-9.	[80]
Uremic Clearance Granules	Radix et rhizoma rhei, Radix astragali, Radix glycyrrhizae, Rhizoma atracylodes macrocephalae, Radix polygoni multiflori preparata, Flos chrysanthemi, Radix salviae miltiorrhizae, Radix codonopsis, Radix bupleuri, Cortex mori, Radix sophorae flavescentis, Radix paeoniae alba, Herba plantaginis, Rhizoma pinelliae, Poria, Rhizoma ligustici.	Adenine administration and UUO	Promote ECM degradation, regulate MMP-2/TIMP-1 balance and TGF- β 1/Smad signal pathway	[27]
Qi Zhu Xie Zhou Fang	Astragalus mongholicus, Atractylodes macrocephala, Coix lacryma-jobi, Pyrrosia lingua, Smilax glabra, Salvia Miltiorrhiza, Cuscuta chinensis, Isaria cicadae	Adenine and potassium oxonate induced hyperuricemic nephropathy model	Decrease fibronectin, collagenI, α -SMA, increase E-cadherin expression	[47]
Qishen Yiqi dropping pills	Radix astragali, Salvia miltiorrhiza, Panaxnotoginseng, rosewood	UUO	Decrease TGF- β 1, α -SMA, collagenI, β -catenin	[81]
Huangqi Decoction	Radix astragali, Wolfiporia extensa, Fructus trichosanthis, Radix ophiopogonis, Shizandra, Liquoric root, Radix rehmanniae	NRK52E, NRK49F UUO HK2 cells	Inhibit TGF- β 1/Smad signal pathway	[29, 82]
Yongui Pill	Radix Rehmanniae Praeparata, Rhizoma Dioscoreae, Fructus Corni, Fructus Lycii, Semen Cuscutae, Cervi cornus colla, Eucommiae cortex, Cinnamomi cortex, Radix Angelicae Sinensis, Radix Aconiti Lateralis Prreparata	UUO NRK-49F	Activate Wnt/ β -catenin Inhibit TGF- β 1/Smad signal pathway	[39]
TI-HU-YIN		UUO	Decrease TGF- β 1 expression	[83]
Huangkui capsule	Abelmoschus manihot	STZ induced DN model	Decrease TGF- β 1, TNF- α , regulate p38MAPK/Akt pathway	[84]

Akt: serine-threonine kinase; BMP: bone morphogenetic protein; CTGF: connective tissue growth factor; DN: diabetic nephropathy; ECM: extracellular matrix; MAPK: mitogen-activated protein kinase; MMP: mitochondrial membrane potential; NRK52E: Normal kidney proximal tubular; NRK49F: renal fibroblast cells; STZ: streptozotocin; TGF- β 1: transforming growth factor- β 1; TIMP-1: tissue inhibitors of metalloproteinase-1; TNF- α : tumor necrosis factor- α ; UUO: unilateral ureteral obstruction; α -SMA: α -smooth muscle actin.

Formula	Constitute	Model / Cell type	Mechanism	Ref
Kangxianling granule	Radix salviae miltiorrhiae, prepared rhubarb, angelica, Achyranthes, peach kernel	UUO	Inhibit TGF- β 1/Smad signal pathway	[37]
Huluba Wan	Trigonella foenum-graecum, Psoralea corylifolia	STZ induced DN model	Reduce oxidative stress via PKC- α /NADPH oxidase signal pathway	[85]
Fufang Xue Shuan Tong capsule	Panax Notoginseng, Radix Astragali, Radix Salvia Miltiorrhizae, Radix Scrophulariaceae	STZ induced DN model	Inhibit BMP2- TGF- β -CTGF signal pathway Reduce oxidative stress	[86, 87]
Wenpitang Hab Wuling san	Codonopsis pilosulae radix, Salviae miltiorrhizae radix, Pinelliae rhizome, Coptis rhizome, Epimedium herba, Rhei radix et rhizoma, Perillae folium, Glycyrrhizae radix, Artemisiae capillaris herba, Alismatis rhizome, Poria, Atractylodis macrocephalae rhizome, Polyporus, Cinnamomi ramulus	UUO	Inhibit TGF- β 1/Smad signal pathway	[74, 88]
Bushen HuoXue formula	Astragali radix, Trigonellae semen, (Rhei radix et rhizoma, Vaccariae semen, Curcumae rhizoma, Smilacis glabrae rhizoma, Coptidis rhizoma	5/6 nephrectomy rats	Decrease TGF- β 1, α -SMA, increase E-cadherin expression	[89]
Shenkang injection	Rhubarb, Astragalus, Radix Salviae Miltiorrhizae, Carthami Flos	5/6 nephrectomy induced CKD model	Reduce oxidative stress through inhibit TGF- β 1/Smad signal pathway	[90]
Yishen Jiangzhuo Granules	Radix et Rhizoma Rhei, Poria, Radix Pseudostellariae, Radix Astragali, Rhizoma Atractylodis Macrocephalae, Fructus Mori, Serissa foetida, Crataegus pinnatifida, Angelica sinensis	5/6 nephrectomy	Inhibit renal tubular epithelial cell apoptosis through inhibiting TGF- β 1-ROS-MAPK signaling	[73]
Danggui Buxue Tang	Radix Angelicae Sinensis, Radix Astragali	UUO	Decrease NLRP3 inflammasome and IL-1 β expression	[91]

ERK1/2: extracellular signal-regulated kinase 1/2; JNK1/2: c-Jun N-terminal kinase 1/2; IL-1 β : interleukin-1 β ; MAPK: mitogen-activated protein kinase; NF- κ B: nuclear factor-Kappa B; NLRP3: NOD-like receptors family pyrin domain-containing 3; ROS: reactive oxygen species; STZ: streptozotocin; TGF- β 1: transforming growth factor- β 1; UUO: unilateral ureteral obstruction; α -SMA: α -smooth muscle actin.

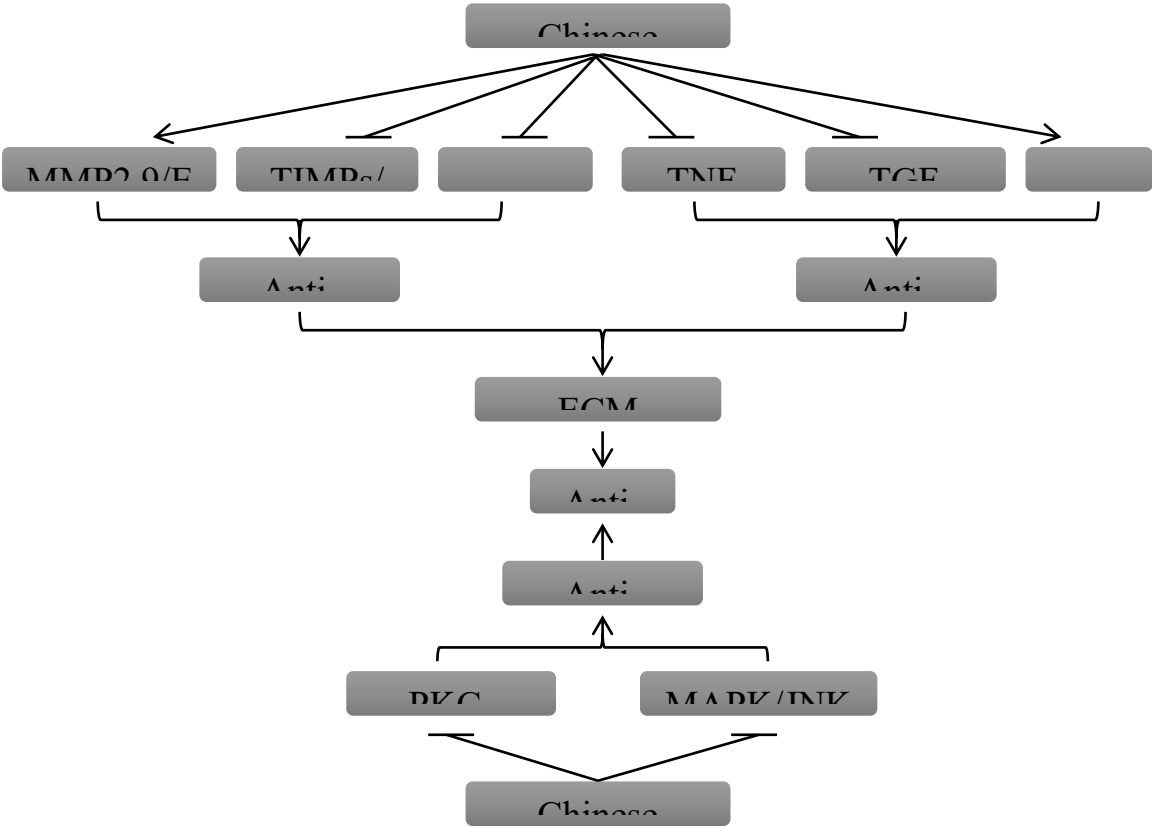


Fig. 1 The schematic diagram of the anti-fibrosis effects of Chinese herbal formulas